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A review on cryptosporidium with other important protozoan parasite diseases of zoonotic importance

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Abstract
Zoonotic protozoan parasites are increasing concern in both developed and developing countries. They are responsible for acute and chronic diarrhoea in immune compromise and immune competent individuals. Several foodborne and waterborne disease outbreak are associated with them which further highlighted their public health importance. This review highlighted the important emerging protozoan parasites Cryptosporidium, Giardia, Cyclospora Microsporidia and Blastocystosis with emphasis on their zoonotic significance.

Keywords: Zoonotic, cryptosporidium, parasite

1. Introduction
Due to the increasing urbanization, growth in global trade (meat, milk and other products of animal origin), population explosionand climatic change have contributed to expanding the impact of zoonotic diseases (Solaymani-Mohammadi and Petri, 2006) [68]. The incidence of foodborne and waterborne disease outbreak are also reported worldwide and incident are on the rise. One of the main reasons for this outbreak can be attributed to zoonotic protozoan parasites. Protozoan parasites are responsible for acute and chronic diarrhoeal disease in both human and animal worldwide, leading to significant morbidity and mortality. The diseases continue to be a significant public health problem in both developed and developing countries especially with increasing population of severely immune compromised individuals due to the AIDS epidemic, cancer chemotherapy and organ transplants. This increased in the prevalence of opportunistic infections has led to the recognition of the disease causing potential of protozoan parasites as human pathogens. Infectious protozoan parasites are transmitted to humans through several routes, including contaminated food and water, inadequately treated sewage/sewage products and livestock and domestic pet handling (Smith *et al*. 1995) [67]. Protozoan parasites are ubiquitous in distribution and their transmission stages (oocysts and cysts, respectively) may remain viable for several months under a range of environmental conditions (DeReignier *et al.,* 1989) [20]. One of their public health importances lies in fact that the environmentally robust oocysts are extremely resistant to the disinfectants commonly used in drinking water treatment (Hibler *et al.,* 1987; Korich *et al.,* 1990; Finch *et al.,* 1993) [34, 42, 29]. Various community outbreaks due to contamination of water or food with these protozoa have further highlighted their importance in public health particularly in developing nations

Cryptosporidium
Cryptosporidiosis is an important emerging zoonotic disease caused by spp Cryptosporidium. It is a small apicomplexon protozoan parasite which inhabits the mucosal epithelium of the gastrointestinal tract of a wide range of vertebrate hosts including man. Cryptosporidium spp. was first described by Tyzzer in 1907 but for several decades, it was not considered important to humans. However, in 1976 the pathogenesis of Cryptosporidium species was first recognised in humans and with the recognition of frequent cases in immune-competent individuals along with the number of waterborne outbreaks has changed this image. In fact, Cryptosporidium is now one of the most commonly identified intestinal pathogens throughout the world.
At present, 20 valid species of Cryptosporidium have been recognised (Egyed *et al.,* 2003; Thompson and Monis, 2004; Xiao *et al.,* 2004; Power and Ryan, 2008) [24, 73, 75, 76, 78, 87, 89, 57].

But the vast majority of illness in human are caused by Cryptosporidium parvum and recognised as the main zoonotic species. The molecular analysis of human and bovine isolates of C. parvum, indicates the existence of two predominantly distinct genotypes (Widmer *et al.,* 1998; Xiao 2010 Xiao and Ryan 2004 and Caccio 2005, Peng *et al.,* 1997) [32, 85, 88, 87, 89, 12, 16, 48, 54]: Type I genotypes (anthroponotic or humans genotype) and Type 2 genotypes (zoonotic or cattle genotype.
Cattle could be infected with at least ten various Cryptosporidium species or genotypes and have been considered the major reservoir of Cryptosporidium spp. for human infections. Calves below one month of age are found to be most susceptible to the infection and major contributors of zoonotic C. parvumthan the other age group (Fayer *et al.* 2006 Tzipori and Ward 2002 and Singh *et al.* 2006) [26, 27, 79, 64]. With the attainment of immunological maturity the infection subsides in older animals though they remain as a source of infection to other susceptible individuals. Its occurrence is dependent on factors that include season, age and other demographic characteristics of a population (Joute *et al*. 2014, Bhat *et al*. 2012, Roy *et al*. 2006) [38, 9, 62].
Infection is caused by ingestion of oocysts along with water or food. The ingested oocyst released sporozoites, which subsequently attached to and infiltrates epithelial cells in the small intestine and result in malabsorptive or secretory diarrhoea. It completes its life cycle in the small intestine and releases enormous amount of robust oocysts which are shed in the faeces of infected people and animal (Adjei *et al.* 2003) [3]. Oocysts of C. parvum are spherical, with a diameter of 4–6mm, and may be either thick- or thin-walled oocysts. Thin-walled oocysts may excyst within the same host and start a new life cycle (autoinfection). Thick-walled oocysts are excreted with the faeces. Cryptosporidium spp. is highly infectious and as low as 30 oocysts can cause infection in healthy volunteers.
In developed countries, various modes of transmission have also been identified like close person to person contact e.g. hospital cross infections and through zoonotic sources (Koch *et al.* 1985) [41]. Contaminated water and food have been implicated as the main source of infection in human and serious outbreaks of cryptosporidiosis such as the Milwaukee outbreak in 1993 (MacKenzie *et al.* 1994) [47]. The contact with infected calves has also been implicated as a major cause of outbreaks among veterinary students and research workers and children attending agricultural camps and fairs (Preiser *et al*., 2003; Smith *et al*., 2004; Chalmers *et al*., 2005) [58, 66, 16]. The micro-organism is ubiquitous in environment (Navin and Junarek 1984) [49]. So, there is every possibility of zoonotic transmission of infection from animals to human beings, especially under poor hygienic condition in developing countries.
Cryptosporidiosis remains one of the most important health problem globally and leading cause of morbidity and mortality especially in developing countries (WHO 2006) [84]. It gives rise to a chronic, life threatening condition particularly in those with Human Immunodeficiency Virus (HIV) and person with acute gastro-enteritis (Pieniazak *et al.* 1999) [55]. Mortality in immunocompetent patients is generally low. In an immune-competent host, the organism usually produces short-term and self-limited diarrhoea, while in immune-deficient individuals or that undergoing cancer chemotherapy infection is often prolonged resulting in significant morbidity due to diarrhoea and dehydration (Aboul-Magd *et al* 2000) [1]. No consistently effective therapeutic agent has been found (Griffiths *et al.* 1998). The prevalence rates of 10 to 33 per cent in those with AIDS have been reported from developing countries. Malnutrition, which impairs cellular immunity, is another recognized risk factor for cryptosporidiosis (Gendrel *et al.* 2003) [30]. It is also reported that pregnancy may predispose to Cryptosporidium infection (Ungar, 1990) [80].
Unlike bacterial pathogens, Cryptosporidium oocysts are resistant to chlorine disinfection and can survive for days in treated recreational water venues (e.g., public and residential swimming pools and community and commercial water parks) (Le Chevallier *et al.* 1991) [44]. Due to the size and frequency of these outbreaks, cryptosporidiosis became a serious public health issue worldwide and prompted re-evaluation of the microbiological standards for drinking water by health authorities in developed and developing countries. The guidelines of World Health Organisation (WHO) for drinking water, classifies Cryptosporidium as a pathogen of significant public health importance (WHO 2006) [84]. The estimated prevalence of Cryptosporidium spp. in people with diarrhoea is 1% to 3% in developed countries and about 10% in developing country (Chen *et al.* 2002) [17].

Giardia

Giardia is known to infect a wide range of host which can cause diarrhoea and ill thrift (Farthing *et al*., 1986; Thompson and Monis, 2004) [25, 73, 75, 76, 78]. Giardia duodenalis is the only species found in human, sometimes referred to as Giardia lamblia or Giardia intestinalis. Molecular assay of Giardia isolates from human and non-human hosts (dogs, cats, livestock and wildlife) has confirmed the existence of seven genetic group (or assemblage) (Monis *et al*., 2009). Assemblages C to H are host-specific and do not infect humans. However assemblages A and B which are found in humans have also been reported from different animal species supporting the potential for zoonotic transmission (Adam, 2001; Thompson, 2004; Xiao *et al*., 2004; Smith *et al*., 2007) [2, 73, 75, 76, 78, 87, 89, 39, 65]. Although actual zoonotic transmission is still not clear. However rare infections and the isolation of zoonotic genotypes from cats and dogs suggest that they are a potential source of human infection that may be acquired through handling, sleeping together, licking, and kissing (Ipankaew *et al*., 2007; Leonhard *et al*., 2007; Traub *et al*., 2004) [37, 45, 78]. The role that wildlife plays in the zoonotic transmission of Giardia is also unclear. Studies of wildlife species have observed infections with assemblages A and B and these have raised questions on the transmission dynamics of this parasite (Fayer *et al*., 2006; Graczyk *et al*., 2002; Thompson *et al*., 2009) [26, 27, 31, 48, 77]. Humans are considered to be the source of infection in non-human primates like dogs, beavers, coyotes and marine mammals, Dixon *et al*., 2008; Thompson *et al*., 2009) [21, 48, 77].
Giardia has a global distribution causing an estimated 280 million human cases yearly from both developed and developing country (Lane and Lloyd, 2002). About 200 million people have asymptomatic giardiasis with some 50,000 new cases reported each year from Asia, Africa and Latin America (WHO, 1996) [83]. The epidemiological distribution of human assemblages of Giardia duodenalis is due largely to exposure to and ingestion of infectious cysts through contaminated food or water. High prevalence rate are reported from developing countries with poor standards of hygiene and sanitation, in day-care centres and nurseries. Incidences of giardiasis are also reported from individuals who are in close contact with dogs, cats, rodents, beavers, or nonhuman primates. Person-to-person transmission is by far

the most common route of transmission of Giardia (Pond *et al*., 2004; Thompson, 2004) [73, 75, 76, 78]. The infective dose for Giardia is between 10 and 100 cysts (Rentdorff, 1954) [61]. The incubation period in humans is typically 1–2 weeks and typical symptoms of Giardia are diarrhoea, bloating and flatulence.

Giardia cysts are excreted in large numbers in the faeces of infected humans and other animals (both symptomatic and asymptomatic). Cysts are infectious when shed in the faeces and can remain infectious for prolonged periods in cool, damp environments, e.g. more than 77 days at less than 10^0C (World Health Organization, 2004) [86]. Giardia cysts are ubiquitous in the environment, commonly found in sewage effluent, surface waters and in shallow springs. Cysts are easily disseminated and are transmissible via the faecal–oral route. However, it is not clear how many of these cysts detected in animal and environmental samples represent strains that are infective to humans (Thompson, 2000) [72].

Giardia poses a great cause of concern to water supplies because of its resistance to chlorination. However, more readily be removed by filtration than Cryptosporidium because of its larger size. The prevalence of the disease varies from 2% to 5% in developed to 20% to 30% in developing countries. The variation in prevalence might be attributed to factors such as the geographical area, the urban or rural setting of the society, age and the socio-economical conditions of the study subject.

Microsporidia

Microsporidia are single-celled, spore-forming obligate intracellular parasites. They are widely distributed in nature which, prior to 1985 was only sporadically reported in humans. Although there are more than 1200 species of microsporidia, only two species are infections to human associated with gastrointestinal disease. Microsporidia spp has been isolated from a wide range of animal hosts including cattle, pigs and a variety of birds suggesting the possibility that this may be zoonotically transmitted (Bornay-llinares *et al*., 1998) [11]. Possible modes of transmission include person-to-person, zoonotic transmission, inhalation of contaminated aerosols and ingestion of contaminated food and water (Lobo ML. *et al*. 2006 Reetz *et al*., 2002) [46, 60]. There has been a dramatic increase in microsporidiosis in humans in the last 20 years in tandem with the AIDS pandemic (Ambroise-Thomas, 2000) [4]. The spectrum of clinical presentation ranges from silent carriers in the immune-competent to severe infections in the immune-depressed patients. Studies have reported the presence of Microsporidia in tertiary sewage effluent, surface water, and groundwater. The study therefore provided evidence that these are waterborne pathogens. However, only one outbreak of microsporidiosis, associated with waterborne transmission, has been reported in the literature (Cotte L. *et al*. 1999) [18].

Cyclospora

Cyclospora is an obligate, intracellular coccidian parasite whose only natural host is humans (Eberhard *et al.,* 2000) [23]. Cyclospora was first recognised as a human pathogen in 1977 (Ashford, 1979) [6] and since then is considered as important emerging disease of public health concern. Among the different species of Cyclospora identified, Cyclosporacayetanensis is the only species found in humans with exception in monkeys and baboons (Eberhard *et al*., 1999) [22]. Initially, it was referred to as cyanobacterium-like bodies but is now classified as Cyclospora sp. (Bendall *et al*., 1993; Ortega *et al*., 1993) [8, 52] The parasite is known to multiplies in the cells lining the small intestine of the host and produce disease (Ortega *et al*., 1997) [51]. The spherical oocyst measuring 8-10 mm in diameter has two sporocysts each with two sporozoites. Unlike other protozoan parasite freshly passed oocysts are not infective. The oocysts requires longer period for the sporulation depending on climatic factors to develop and mature in the environment hence, fecal-oral transmission is unlikely (Sterling and Ortega 1999) [70]. Epidemiological data indicate that Cyclosporaspp are transmitted by water and food (Hoce *et al*., 1993; Centers for Disease Control and Prevention 1997) [36, 15] Clinical illness is characterized by persistent diarrhea, bloating, flatulence, abdominal cramps, constipation, and fatigue. In immunocompetent individuals the symptoms are self-limiting but in immunocompromised patients the disease may be prolonged that could be life threatening (Karanja *et al*., 2007) [40]. Oocyst are excreted in associated with clinical illness (Shlim *et al*., 1991) [63] Several endemic cases due to Cyclospora spp were reported from Haiti, Nepal and Peru (Eberhard *et al*., 1999) [22] In north America and Europe cyclosporiasis is associated with overseas travel and travellers returning from developing nations (Verweij *et al*., 2003, Swaminathan *et al*., 2009) [82, 71]. However, non-travel-related cases of cyclosporiasis have been reported in several developed countries. Cyclospora has been associated with several waterborne and foodborne outbreaks worldwide. Food-borne outbreaks have been reported in North America and Germany (Verma *et al*., 2003, Ho *et al*., 2002) [82, 35]. The largest outbreaks of foodborne disease occurred during the late 1990s in North America associated with the consumption of fresh raspberries imported from Guatemala. A significant reservoir of C. cayetanensis has yet to be identified in animals. Transmission is likely through food and water that have been contaminated with human faeces.

Blastocystosis

Blastocystosis is an important emerging disease of zoonotic importance Boorom *et al*., 2008; Parkar *et al*., 2010) [10, 53]. However the taxonomic classification as well as the pathogenicity of Blastocystis is still not clear. A wide range of animals e.g. mammals, birds, reptiles, amphibians, arthropods are known to be reservoir of this infection (Thompson 2011) [74] The most common symptoms associated with this parasite are diarrhoea, abdominal pains, and vomiting. While the organism has a global distribution, the prevalence is higher in developing countries (Stenzel *et al*., 1996) [69] Poor hygiene and sanitation facilities are known to be the major contributing factors and travelers and immigrants to developing tropical countries are at risk to diarrhea due to Blastocystis. It is associated frequently with diarrhoea in immunosuppressed patients organ transplant patients and patients with irritable bowel syndrome (Zierdt 1991) [90] It has been reported in renal transplant patients in India (Rao *et al*., 2003) [59].

Waterborne and foodborne outbreaks

Parasitic protozoa have been recognised as having great potential to cause waterborne and foodborne disease. Several outbreaks have been associated with parasitic protozoa worldwide. Although other parasitic protozoa can be spread by food or water, current epidemiological evidence suggests that Cryptosporidium, Cyclospora and Giardia present the largest risks. (Dawson 2005) [19] They are widespread in the environment, particularly the aquatic environment, and major outbreaks occurred as a result of contaminated drinking water especially cryptosporidiosis and giardiasis. The organisms are also of great concern in food production worldwide. Parasitic protozoa do not multiply in foods, but they may survive in or on moist foods for months in cool, damp environments. However outbreaks of foodborne disease have occurred but tended to involve fewer reported cases than those attributed to the drinking water supply. Worldwide Report of outbreaks due to the waterborne transmission of parasitic protozoa during the time period from 2004 to 2010 Cryptosporidium spp. was reported to be most common waterborne parasite responsible for 60% of the outbreak followed by Giardia lamblia 35.2% and other protozoa in 4.5%. More than 160 waterborne outbreaks of cryptosporidiosis and giardiasis have been reported worldwide, with most cases reported in the US and UK.

Cryptosporidium has been implicated as the cause of numerous outbreaks of watery diarrhea associated with contaminated food or water supplies (Fayer *et al.* 2000) [28] and some cases of water-borne transmission have been linked to domestic livestock, especially cattle. Water is the most commonly reported vehicle of transmission in Cryptosporidium outbreaks. For example, in a review of 89 waterborne outbreaks of infectious intestinal disease (IID) involving 4321 cases in England and Wales, Cryptosporidium was the causative agent in 69% The largest documented outbreak of gastrointestinal disease due Cryptosporidium occurred in Milwaukee, Wisconsin, USA, in 1993, during which there were an estimated 403,000 cases of illness as a result of a contaminated drinking water supply (Mackenzie *et al*., 1994) [47]. In recreational waters, Cryptosporidium is also the leading microbial cause of outbreaks in both the UK and USA. One of these occurred in Sydney, Australia, in 1994, when 70 people contracted cryptosporidiosis. Most Cryptosporidium drinking water outbreaks are attributed to chronic filtration failures or livestock and rainfall in the catchment. Cattle are a significant source of C. parvum in surface waters. During a waterborne outbreak of cryptosporidiosis in British Columbia, oocysts were detected in 70% of the cattle faecal specimens collected in the watershed close to the reservoir intake (Ong *et al*., 1997) [50]. Several outbreaks have occurred in close social groups such as households, nurseries, and hospital or nursing home settings. Cryptosporidium transmission occurs frequently in nurseries, where infants are clustered within classrooms, and share toilets and play areas. An outbreak was reported in a bone marrow transplant unit when five patients developed cryptosporidiosis after an infected patient was admitted to the unit (Casemore 1990) [14]. Foodborne outbreak of cryptosporidiosis on larger scale occurred in the USA in 1993 arising from the consumption of infected fresh-pressed apple cider.

Waterborne outbreak of giardiasis was documented since 1970s. Since then Giardia is one of the most frequently implicated organism in waterborne disease outbreak. Between 1965 and 1984, some 90 outbreaks with a total of 23,776 cases were reported in the United States (Flanagan, 1992). Between 1992 and 1997, surveillance carried out by 43 states in the United States indicated that as many as 2.5 million cases of giardiasis occur annually in that country. Giardia was the most commonly reported causative agent associated with infectious disease outbreaks related to drinking water in Canada. Contamination of source waters from human sewage and inadequate treatment (e.g., poor or no filtration, relying solely on chlorination) appear to have been major contributing factors. A number of outbreaks of foodborne giardiasis related to food preparation have been documented, probably caused by infected food handlers or contact by food handlers with infected people, particularly children.

Cyclospora has only been documented as a significant human pathogen since the early 1990s. The first outbreak of cyclosporiasis to be associated with drinking water occurred among hospital staff in Chicago, Illinois (Karanis *et al*., 2007) [39]. The outbreak was linked to a chlorinated water supply suggesting that C. cayetanensis is resistant to levels of chlorine used in drinking water treatment. It has been recognized in developed countries as the causative agent of a few gastrointestinal outbreaks associated with fresh (unprocessed) food produce, i.e. soft fruits and leafy vegetables. Several foodborne and waterborne disease due to Cyclosporahas been reported, but not to the same extent as with Cryptosporidium and Giardia.

Microspridia is transmitted by consumption of contaminated food or water as well as spore inhalation. The first foodborne microsporidiosis outbreak has been reported recently from Sweden associated with cucumber consumption. A report of gastrointestinal outbreaks due to Microspridia is scares, despite the detection of Microspridia from water sources.

Conclusions

Protozoan parasites are responsible for a significant public health impact because of the high prevalence and severity of the infection. Its inclination in causing major food and waterborne disease outbreaks have become a great burden among medical practitioner, food producers, veterinarian and wildlife personnel. Although these parasitic infections are distributed worldwide, their prevalence is higher in developing compared to developed countries. However the relative importance of zoonotic infections specially developing countries has not been studied in detail. Disease surveillance and case reporting from both human and animal along with advance disease diagnostic technique are necessary in studying the disease condition and better understanding of their zoonotic importance. Better communication and cooperation among medical and veterinary personnel are necessary in future to know the status of the disease and to formulate control strategies.

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