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REVIEW ARTICLE

Cryptosporidiosis: A Foodborne Zoonotic Disease of Farm Animals and Humans

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ABSTRACT

Globally, the major concerns that are related to morbidity and high rates of death in the human community are foodborne illnesses. *Cryptosporidium* is a significant foodborne zoonotic parasite that is one of the most typical causes of diarrhea in the globe. Approximately 40 different species have been identified as being capable of inflicting severe to moderate illness in people, with *Cryptosporidium hominis* and *Cryptosporidium parvum* serving as the primary disease-causing agents. The main zoonotic reservoirs for Cryptosporidium are domestic animals like cattle and humans. Ingestion of oocyst from animal to person or person to person, fecal-oral transmission as well as consumption of tainted water and food, are all ways involved in disease transmission. Infected food materials like lettuce, cabbage, salad, spinach, radish, parsley, tomato, raspberries, strawberries, etc. showed different prevalence ranges of Cryptosporidium. The only medication authorized to treat cryptosporidiosis at this time is nitazoxanide. Other medications including paromomycin, azithromycin, rifaximin, and halofuginone have also been used due to clinical effectiveness. In humans, the disease severity of Cryptosporidium outbreaks ranges from 0.9% (Kuwait) to 39.6% (Iraq). This review emphasizes the significance of foodborne zoonosis in humans and farm animals by describing the transmission rate of Cryptosporidium from different sources and the presence of different percentages in food material.

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1. Introduction

Global burden of foodborne illnesses caused by microbes, parasites, and chemicals is significant (CDC, 2016). Enteric infectious agents are responsible for major losses caused by foodborne illnesses as 550 million cases out of a total of 600 million in 2010 were due to foodborne illnesses according to the World Health Organization (WHO, 2015). Losses due to foodborne illnesses per year have been estimated to be 10-83 billion USD in the USA, 86 million USD in New Zealand, and 1.289 million USD in Australia (Ryan *et al*., 2018a). In developing and underdeveloped countries, intestinal parasites are recognized as a critical public health concern for both animals and humans (Haghi *et al*., 2020). Cryptosporidiosis is a foodborne and waterborne diarrheal illness caused by Cryptosporidium species. More than 8 million cases of foodborne cryptosporidiosis are reported annually (Ryan *et al*., 2018b). Cryptosporidium was ranked fifth out of 24 potential foodborne parasites by the joint venture of FAO and WHO (FAO/WHO, 2014). It is a zoonotic disease that globally affects people. Cryptosporidiosis is prevalent in humans along with 150 mammalian species. It is also found in amphibians, fish, reptiles, and birds. In immunocompromised individuals, especially children, the infection can worsen the situation resulting in mortality (Yılmazer *et al*., 2017). It usually manifests as a gastrointestinal disorder. It is a clinical syndrome caused by Apicomplexan genus Cryptosporidium (Chalmers and Davies, 2010). More than 17 species of Cryptosporidium can cause infection in humans while *C. hominis* and *C. parvum* are mainly responsible for causing cryptosporidiosis in humans (Ryan *et al*., 2018b). Transmission of *C. hominis* is primarily anthroponotic while *C. parvum* is zoonotic as it involves numerous hosts (Manjunatha *et al*., 2016). Many Cryptosporidium species are found among which 40 species have been recognized until now. *C. felis*, *C. canis*, *C. meleagridis*, *C. muris*, *C. viatorum*, *C. ubiquitum*, and *C. cuniculus* are less ordinarily recognized species (Innes *et al*., 2020).

This disease causes severe diarrhea in young animals while mortality is higher in kids and is less severe in lambs (Shanmathi *et al*., 2020). Clinical signs of cryptosporidiosis include dehydration, diarrhea and abdominal pain. This condition can worsen in persons with nutritional deficiencies and acquired immunodeficiency syndrome (AIDS) (Mor *et al*., 2010). Edward Tyzzer (1875-1965) in 1907 first investigated the parasite in the gastric glands of common mice (*Mus musculus*) and reported the genus Cryptosporidium (Galván-Díaz, 2018). During the 1970s, it was observed both in humans and animals as a diarrheal syndrome (Cacciò and Putignani, 2014). It is prevalent globally but mostly found in moist and humid seasons (Khan *et al*., 2017). In developed countries, the prevalence of Cryptosporidium ranges from less than 1 to 3% while in developing countries it ranges from 5% to more than 10% (Khushdil *et al*., 2016a). This protozoan has a complicated life cycle that primarily develops in epithelial cells of the digestive tract. It involves a large number of hosts which comprises fish, reptiles, birds, livestock, humans, and all wildlife. The fecal route is the most common route of transmission through direct or indirect contact with Cryptosporidium oocyst. It occurs via zoonotic, airborne, foodborne, waterborne routes, and person-to-person contact (Mahmoudi *et al*., 2017).

In domestic animals and humans, cryptosporidiosis has been designated as the sixth major foodborne parasitic infection worldwide (Zueter, 2020). The predominant source of zoonotic Cryptosporidium includes livestock specifically cattle. Cases of cryptosporidiosis have been seen in all continents in significant numbers of livestock species comprising goats, sheep, horses, camels, ducks, pigs, asses, chickens, and buffaloes with exception of Antarctica. A significant decline in the economy and production of the livestock industry results due to Cryptosporidium infection (Vermeulen *et al*., 2017). It occurs due to enhanced animal health care expenditures, raised labor costs and animal services, reduction in the life span of animals, and declined animal growth rate (Pumipuntu and Piratae, 2018). Recently, the most often employed genetic marker in studies of genetic divergence, transmission passage, source of infection and host adoption of Cryptosporidium is the DNA sequence analysis of the 60-kDa glycoprotein gene (gp60) (Kiani *et al*., 2017). Various diagnostic methods have been developed to identify Cryptosporidium in feces from sheep, cattle, and horses. These diagnostic methods consist of enzyme-linked immunosorbent assay (ELISA), molecular methods (nested polymerized chain reaction PCR), microscopy (Kinyoun's staining), and immunology (Direct Fluorescence Antibody tests or DFAT) (Mirhashemi *et al*., 2015a).

Clinical studies have been conducted on a variety of medications such as paromomycin, rifabutin, nitazoxanide, and numerous macrolides (spiramycin, azithromycin, clarithromycin) (Abubakar *et al*., 2007). The one health approach contends that human health is correlated with animal health and the environment, and animals play a crucial role in the dynamics of Cryptosporidium oocyst propagation (Taghipour *et al*., 2020). Schwabe (1984) defined "one medicine" as One health approach to tackle the zoonotic disease that is a global approach to promote health and wellbeing by alleviation and prohibition of disease risk which proceed at the connection between animal, human, and the environment. This paper will describe the one health strategy for prophylactic inhibition of cryptosporidiosis, which involves the significance of comprehending zoonotic and non-zoonotic transmission, environmental risk factors, life cycle, enhanced diagnosis, and detection and therapy (Ryan *et al*., 2016a).

2. Epidemiology of cryptosporidiosis

The prevalence of Cryptosporidium spp in Malaysia, Saudi Arabia, China, Pakistan, Iran, Egypt, India, and Jordan was estimated to be roughly 5.2, 8.5, 11, 9-20, 1.5-7, 38.25, 11.8, and 8.3% respectively (Meamar *et al*., 2007; Iqbal *et al*., 2012; Helmy *et al*., 2013; Hijjawi *et al*., 2016; Zaheer *et al*., 2021). Outbreaks of human Cryptosporidium in different countries have been documented in Table 1.

Table 1: Reports of human Cryptosporidium cases in different countries.

Country	Year of Outbreak	References
America	1987, 1993, 2005, 2007, 2008, 2009, 2014, 2017	(Gharpure *et al*., 2019); (Alleyne *et al*., 2020)
Canada	1996, 2001	(Iqbal *et al*., 2015a); (Guy *et al*., 2021)
New Zealand	2020	(Garcia-R *et al*., 2020a)
Pakistan	2010, 2014, 2016	(Raja *et al*., 2014); (Khushdil *et al*., 2016b)
India	2010, 2014	(Sarkar *et al*., 2014)
France	2006, 2009, 2017, 2019	(Costa *et al*., 2020)
Kuwait	2001, 2005	(Majeed *et al*., 2018)

3. Clinical manifestation

Depending on the immunological health, diet, genetics, and location of the infection, the host's age, as well as the species of Cryptosporidium causing the illness, symptoms can range from moderate to drastic (Morris *et al*., 2019). Clinical symptoms in addition to diarrhea include reduction in weight, nausea, vomiting, cramps, appetite loss, and fever. But symptoms can worsen and become more drastic in immunocompromised individuals. The parasite in rare circumstances can invade other organs involving respiratory organs, the liver, the pancreas, and the gall bladder (Shaposhnik *et al*., 2019). Oocysts are secreted for four weeks after the symptoms have typically subsided after one to two weeks. Due to the oocysts' capacity to excyst in the gastrointestinal system and result in autoinfection, chronic infections may develop. Immunocompromised individuals may experience extended or life-threatening illness as a result of infection (Benschop *et al*., 2017). Calves and other young ruminants who suffer from severe to fatal newborn diarrheal syndrome in farm animals are caused by Cryptosporidium, which causes significant direct and indirect economic losses. Long-term detrimental impacts of cryptosporidiosis on animals include decreased productivity and weight increase in sheep and cattle (Zhu *et al*., 2021).

4. Life cycle of cryptosporidium

Cryptosporidium oocysts are approximately 4-6 µm in diameter, tiny, and spherical to ovoid in shape. Cryptosporidium life cycle is accomplished in a single host (Rossle and Latif, 2013). Cryptosporidium life cycle encompasses both sexual and asexual reproduction, and it only takes place in a single host (monoxenous) (Miyamoto and Eckmann, 2015). Each sporulated oocyst contains 4 infectious sporozoites which are found in contaminated food or water. Ingestion of these oocysts starts the infection. In the gastrointestinal tract, infectious sporozoites are discharged during excystation, where they bind to the apical surfaces of host cells. By active invasion mechanism, sporozoites penetrate into plasmalemma of the host cell, where they develop a parasitophorous vacuole (Khan *et al*., 2018). At the point of junction, between cell and parasite, a feeder organelle establishes giving the parasite the ability to take nutrients from its host (Relat and O'Connor, 2020).

The sporozoite itself develops into a trophozoite and takes on a more spherical shape followed by the formation of feeder organelle (Thomson *et al*., 2017). Trophozoite develops into a mature type I meront containing eight merozoites after undergoing three rounds of asexual reproduction (merogony). To produce more type I meronts or to change into type II meronts, which contain four merozoites, the merozoites released from the type I meront infect nearby intestinal epithelial cells (Pinto and Vinayak, 2021). Type II meronts' merozoites, infecting the intestinal epithelial cells, engage in sexual reproduction to create micro and macro gametes. The union of these gametes results in the formation of the zygote that matures into oocysts (Wang *et al*., 2021). The zygote either produces a thick-walled oocyst with a two-layered membrane coating or a thin-walled oocyst with single layered membrane coating after undergoing two mitotic divisions (Fig. 1).

By bursting and secreting infectious sporozoites, thin-walled oocysts can induce reinfection within the gastrointestinal system of the same host, in contrast to the thick-walled oocysts that tolerate inappropriate environmental conditions for months and are expelled through feces (Pumipuntu and Piratae, 2018). It is believed that autoinfection accounts for the rise in illness severity in immunocompromised individuals. Three different processes have been proposed to explain symptoms: Inflammatory cells impregnating the lamina propria is the first sign, followed by the enhanced permeability of the epithelial layer, villous deterioration, and cell death. It finally leads to malabsorption brought on by the destruction of the intestinal wall. To maintain the continuity of infection and to prevent the infected cell from going through apoptosis, Cryptosporidium might alter the immunological response (Janssen and Snowden, 2021).

5. Transmission

Transmission of Cryptosporidium can occur mainly through the following pathways (Fig. 2):

- Through ingesting the oocyst-contaminated water and food (fecal-oral route).
- Direct animal to human transmission (zoonotic). Direct person to person transmission (anthroponotic) (Ayinmode *et al*., 2018).

5.1. Indirect transmission

Indirect transmission of oocysts poses a major hazard, especially in well-established countries. It occurs when an infection transmits by contaminating nearby water supplies or food, and mechanical transfer of oocyst by, for instance, flies and animals like dogs and livestock. Inadequate hygiene plays a significant contributing role in the transfer of intestinal protozoa like Cryptosporidium (Thompson *et al*., 2016).

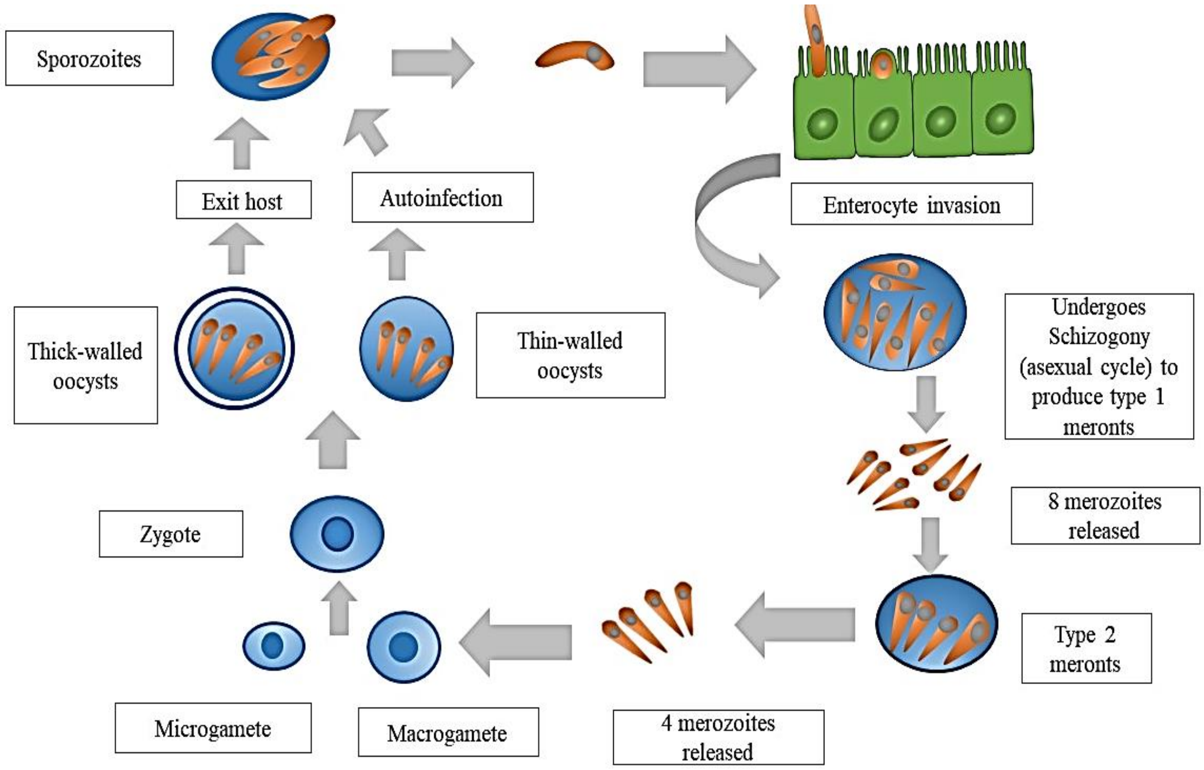

Fig. 1: Life cycle of Cryptosporidium involves different stages.

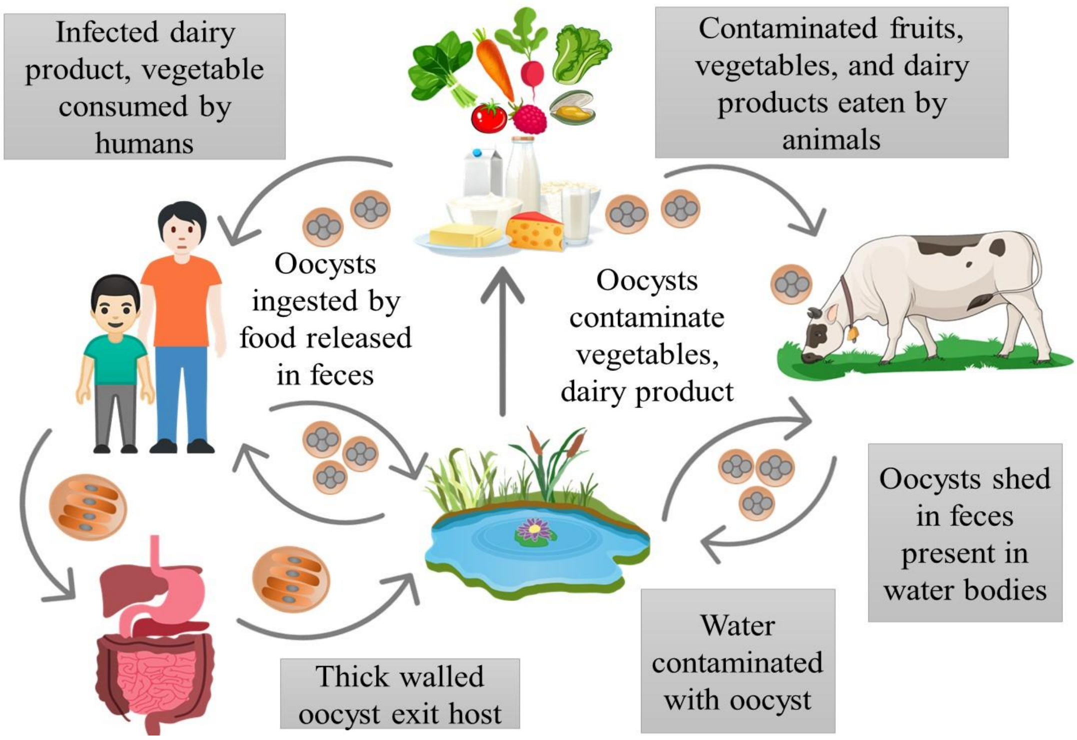

Fig. 2: Possible transmission pathways of Cryptosporidium.

5.2. Person to person transmission

The parasite can be transmitted primarily from one person to another by swimming, drinking contaminated water, eating spoiled, inadequately washed, and raw foods including fruits and vegetables, through spores in respiratory infections, and if objects like hands or surfaces are spoiled with fecal wastes of infected animals or humans or both (Chukwuma Sr, 2019).

5.3. Zoonotic transmission

The early Cryptosporidium epidemics were zoonotic in origin. A youngster who resided on a farm where cattle are raised was the first victim of the disease (Chalmers and Giles, 2010). Several factors contribute to the transfer of this zoonotic disease which include animal wastes, inadequate hand washing, lambs, and calves (Vanathy *et al*., 2017).

5.4. Waterborne transmission

The ingestion of polluted drinking water from swimming pools as well as from ground sources or surface sources contributed to waterborne epidemics. Malfunctioning of drinking water treatment facilities, water leakage in the distribution systems, and infected sewage are all the ways through which Cryptosporidium oocysts might get into the drinking water sources (Nasser, 2016).

5.5. Foodborne zoonosis

According to the method of transmission to humans, there are generally two major groupings that may be used to classify foodborne parasites. Consumption of uncooked infected food is the most common source of zoonotic transmission. Infected food includes tainted water and food sources, vegetables, or animal muscle tissues. Consumption of water and food contaminated with oocysts is responsible for the spread of cryptosporidiosis, which is known to be extremely resistant to treatment methods. The first food-borne outbreak caused by *C. parvum* was reported in Finland. The outbreak occurred among persons who had eaten from a canteen, and a salad mixture was suspected to be a source (Pönka *et al*., 2009). Also, Cryptosporidium oocysts were detected in 4.69% of vegetable samples, but not in any fruit samples (Chukwuma Sr, 2019). In Norway, samples of various fruits and vegetables were analyzed and only 4% of samples were found contaminated with protozoans, of which 26% were lettuce, and 74% were mung bean sprouts (Rzeżutka *et al.*, 2010; Ranjbar-Bahadori *et al.*, 2013).

A wide range of foods, including dairy products, meat, many types of shellfish, and vegetables have been shown to contain oocysts of Cryptosporidium. Outbreaks of foodborne cryptosporidiosis are also associated with fresh vegetables (especially salads), apple cider, and dairy products (Ryan *et al*., 2018a) (Table 2).

6. Cryptosporidiosis in animals

By age and geographic distribution, different Cryptosporidium species are more or less prevalent in cattle (Naguib *et al*., 2018). In England and Wales, the frequency of Cryptosporidium in cattle has been reported to be 10.2%, (Smith *et al*., 2014) but in a study screening the farms suspected of being the source of human cases, the prevalence in cattle was reported to be 53% (Smith *et al*., 2010). The findings also revealed that Cryptosporidium prevalence was on average low in horses and goats (20-25%), chicken, guinea pigs, rabbits, and other birds (4-7%), and greater in pigs and sheep (40-50%) (Smith *et al*., 2010). According to several studies, positive farms had a progressive frequency of 100% among young animals (Hotchkiss *et al*., 2015). Cattle are

Table 2: Reports of outbreaks of Cryptosporidium in different regions of the world.

Infected food material	Cryptosporidium prevalence (%)	Year of outbreak	Outbreak region	References
Vegetables	27	2015	Iran (Ilam)	(Avazpoor *et al*., 2015)
Lettuce	40			
Avocado, lettuce, carrot, cabbage, mango, tomato, green pepper, banana	Overall prevalence 4.72	2014	Ethiopia (Arba Minch town)	(Bekele *et al*., 2017)
Perilla leaves	6.9	2015	Korea	(Sim *et al*., 2017)
Sprouts	1.4			
Chives	17.8			
Cherry tomatoes	6.8			
Blueberries	6.8			
Potatoes	0	2012	Korea (Seoul)	(Hong *et al*., 2014)
Spinach	0			
Winter grown cabbage	33.3			
Radish, lettuce coriander leaves, tomatoes, chili, fenugreek leaves, carrot, turnip, cabbage, mint leaves, cucumber	Overall prevalence 6	2016	India (Chandigarh)	(Utaaker *et al*., 2017)
Fluted pumpkin (Ugwu)	44	2011	Nigeria (Kaduna)	(Maikai *et al*., 2013)
Jute mallow (Ayoyo)	40			
Waterleaf	36			
Spinach	0.26	2015	Canada	(Lalonde and Gajadhar, 2016)
Arugula	0.93			
Parsley	86	July 2013-February 2014	Libya (Kufra)	(Saaed and Ongerth, 2019)
Tomato	60			
Watercress	90			
Cucumber	72			
Lettuce	96			
Mint, Oregano Savory, radish, parsley, spinach, tarragon, basil, chives, coriander	Overall prevalence 21.42	2019	Iran (Tonekabon)	(Taghipour *et al*., 2019)
Carrot, radish, lettuce, parsley, coriander	Overall prevalence 3	March 2017-January 2018	Morocco (Marrakech)	(Berrouch *et al*., 2020)
Kale cabbage, Iceberg lettuce, oak leaf lettuce, romaine lettuce	Organic farming 7.7, Conventional farming 7.8	2021	Spain (Valencia)	(Trelis *et al*., 2022)
Raw sheep milk	2.50	2019-2020	Iran	(Abdollahzadeh *et al*., 2022)
Raw cow milk	4.76			
Cilantro	2.0	2001-2002	Costa Rica	(Calvo *et al*., 2004)
Blackberries	6.0			
Strawberries	0			
Raw vegetables	12.1	2021	Pakistan	(Abbas *et al*., 2022)
Green mussels	8.3	November 2006-February 2007	Thailand (Bangkok)	(Srisuphanunt *et al*., 2009)
Sea mullet, Common blow fish, King George whiting, School whiting, Yellow-eyed mullet	Overall prevalence 2.4	2008	Australia	(Reid *et al*., 2010)
Oysters	10	2005-2006	Brazil (Sa˜o Paulo)	(Guiguet Leal *et al*., 2008)
Cockles	50			
Chicken	17.5	2017	China (Wuhan)	(Liao *et al*., 2018)

mostly infected with *C. andersoni, C. ryanae, C. bovis,* and *C. parvum* species (Zahedi and Ryan, 2020). Adult cattle are mostly infected with *C. andersoni*, pre-weaned animals mostly acquire infection of *C. pavrum* while mostly post-weaned animals and young stock tend to have *C. ryanae* and *C. bovis* (Benhouda *et al*., 2017).

In Australia, marsupials like wallabies, koalas, and kangaroos are known to be infected with species such as *C. macropodum* and *C. fayeri* (Khan *et al*., 2018). Globally, various species of Cryptosporidium have been detected in sheep. Among these, *C. ubiquitum, C. parvum,* and *C. xiaoi* occur abundantly, while *C. parvum* and *C. xiaoi* are mostly observed in goats (Alali *et al*., 2021). In cats and dogs, *C. felis* and *C. canis* are the predominant species (Alali *et al*., 2021). Potential zoonotic species frequently found in pigs are *C. scrofarum* and *C. suis* (Zhang *et al*., 2021). The first case of cryptosporidiosis in birds was reported in 1929 (Ryan *et al*., 2021).

C. meleagridis, the first avian species was not recognized till 1955 in Turkeys. The parasite is found less frequently in poultry and abundantly in wild birds as it has a wide variety of hosts (Li *et al*., 2021). *C. meleagridis, C. bailey*, and *C. galli* are the three primary species of Cryptosporidium that have been identified in birds. The only known hazard to humans is *C. meleagridis* which affects parrots and turkeys. Recently investigated species, *C. galli*, infects a variety of hosts such as domestic chickens, pine grosbeaks, and finches whereas *C. baileyi* is probably the most prevalent species of Cryptosporidium due to its capability to infect a variety of birds including feral pigeons, love birds, domestic and caged chickens, ducks, geese and turkeys (Jasim and Marhoon, 2015).

7. Cryptosporidiosis in humans and children

Almost 20 of the genotypes and species of Cryptosporidium have been detected in humans (Table 3). Moreover, the most prevalent are *C. hominis* and *C. parvum*. Furthermore, *C. ubiquitum* and *C. cuniculus* are often observed in patients in certain well-developed countries. Whereas *C. canis*, *C. felis*, *C. viatorum*, and *C.*

meleagridis are usually detected in individuals and youngsters infected with AIDS in underdeveloped countries (Guo *et al*., 2021). A growing number of people are moving into parts of Africa that are home to wildlife such as Nigeria, and this is expected to enhance the spread of zoonotic pathogens like *C. ubiquitum* (Squire and Ryan, 2017).

C. hominis is the principal species involved in anthroponotic transmission as it is primarily a human infection. Since cattle serves as a main source while a variety of animal species serves as the reservoir for *C. parvum*. Zoonotic transmission is thought to be a common method of dissemination (Garcia-R *et al*., 2020b). The findings imply that two main species of Cryptosporidium that attack children are *C. parvum* and *C. hominis*. Other Cryptosporidium species, such as *C. meleagridis* 1/35 (2.9%) and *C. muris* 1/35 (2.9%) from Saudi Arabia, *C. parvum* and *C. felis* from India, have been identified in youngsters in Asia (Mahmoudi *et al*., 2017). The prevalence of Cryptosporidium in different types of patients including adults and children has been indicated in Table 4.

Table 3: Different species of Cryptosporidium in humans and animals.

Sr.	Species Name	Host (Animals and humans)	References
1.	*C. rubeyi*	Squirrels	(Zahedi *et al*., 2016)
2.	*C. canis*	Dogs	(Feng *et al*., 2018)
3.	*C. hominis*	Humans	(Bamaiyi and Redhuan, 2016)
4.	*C. meleagridis*	Birds, humans	(Leitch and He, 2011)
5.	*C. molnari*	Fish	(Rossle and Latif, 2013)
6.	*C. ubiquitum*	ruminants, rodents, and primates	(Xiao and Cama, 2018)
7.	*C. muris*	Rodents, humans	(Ryan *et al*., 2014b; Chappell *et al*., 2015)
8.	*C. suis*	Pig	(Zhang *et al*., 2021)
9.	*C. serpentis*	Corn Snake	(Fayer, 2010b)
10.	*C. cuniculus*	Rabbits	(Xiao and Feng, 2017)
11.	*C. ryanae*	Cattle	(Zahedi *et al*., 2016)
12.	*C. ducismarci*	Tortoises	(Rostad *et al*., 2019)
13.	*C. parvum*	Cattle and other livestock, humans	(Thompson *et al*., 2008)
14.	*C. baileyi*	avian hosts, such as turkeys, ducks	(Wang *et al*., 2021)
15.	*C. felis*	Cats	(Leitch and He, 2011)
16.	*C. galli*	Birds	(Xiao and Cama, 2018)
17.	*C. nasorum*	Fish	(Levine, 1984)
18.	*C. occultus*	Rodents	(Ong *et al*., 2002)
19.	*C. erinacei*	Hedgehogs, humans	(Kváč *et al*., 2014; Garcia-R *et al*., 2020b)
20.	*C. sciurinum*	Red squirrels	(Prediger *et al*., 2021)
21.	*C. myocastoris*	Nutria	(Ježková *et al*., 2021a)
22.	*C. alticolis*	Common voles	(Horčičková *et al*., 2019)
23.	*C. microti*	Common voles	(Horčičková *et al*., 2019)
24.	*C. abrahamseni*	Fish	(Zahedi *et al*., 2021)
25.	*C. bollandi*	Fish	(Bolland *et al*., 2020)
26.	*C. apodemi*	Rats	(Čondlová *et al*., 2018)
27.	*C. ditrichi*	Rodents, humans	(Beser *et al*., 2020; Čondlová *et al*., 2018)
28.	*C. proventriculi*	Birds	(Holubová *et al*., 2019)
29.	*C. ornithophilus*	Ostrich	(Holubová *et al*., 2020)
30.	*C. tyzzeri*	Mice, humans	(Ren *et al*., 2012; Garcia-R *et al*., 2020a)
31.	*C. xiaoi*	Humans, goat and sheep	(Fayer *et al*., 2010; Fayer and Santín, 2009)
32.	*C. andersoni*	Cattle	(Gong *et al*., 2017)
33.	*C. bovis*	Cattle, human	(Fayer *et al*., 2005; Higuera *et al*., 2020)
34.	*C. ratti*	Rats	(Ježková *et al*., 2021b)
35.	*C. macropodum*	Marsupials	(Power and Ryan, 2008)
36.	*C. varanii*	Pet reptiles	(Pedraza-Díaz *et al*., 2009)

8. How cryptosporidiosis affects humans and animals

Until now, 31 different species of Cryptosporidium (including amphibians, reptiles, mammals, fish, and birds) have been identified depending on molecular, biological, and morphological evidence (Ryan *et al*., 2014a). Furthermore, descriptions of over 40 genotypes from distinct vertebrate hosts have been made. *C. parvum* and *C. hominis* accounting for greater than 90% of cases are considerable human infectious agents (Fayer, 2010a; Xiao, 2010). By consuming infective oocysts through the fecal-oral route, people can directly acquire infection. This can happen on the job (Nic Lochlainn *et al*., 2019), by exposure with diseased animals (Hunter and Thompson, 2005), or inadvertently by consuming tainted food or water (Betancourt and Rose, 2004; Hazards *et al*., 2018). Reports regarding data on proportional source attribution for Cryptosporidium are few. In one Canadian study that used exposure data to determine the cause of sporadic cryptosporidiosis, water was the main frequently documented reservoir of infection (48% cases) accompanied by 15% person to person transmission, 8% foodborne zoonosis, 8% exposure with pets, and 21% contact with farm animals (Majowicz *et al*., 2001).

This sequence is largely supported by recent reports (Hald *et al*., 2016). For human cryptosporidiosis, widespread economic and social zoonotic hazardous factors have also been investigated. *C. parvum* was more prevalent in regions with higher concentrations of ruminant livestock and lower densities of the human population, as well as regions with more farms and private water supplies per resident than elsewhere (Pollock *et al*., 2010). For Cryptosporidium, residing areas with a high application rate of manure were linked to the prevalence of *C. parvum* in that region (Lake *et al*., 2007). Furthermore, the diverse transmission and distribution of cryptosporidiosis are illustrated by the recognition of infective species and their subtypes. It allows for the direct application of strategies such as monitoring of hygiene and sanitation measures in homes, institutions, and animal farms along with transportable food chains or recreational water. *C. parvum* anthroponotic has been postulated as human adapted sub-species though the majority of *C. parvum* sub-species are zoonotic (Nader *et al*., 2019). Geographical research reveals that some subtypes of *C. parvum* and *C. hominis* are substantially more prevalent in countries with few resources but zoonotic *C. parvum* dominates in the Europe, Australia, North America, and areas of the Middle East (King *et al*., 2019).

9. Detection and diagnosis of cryptosporidium on food and feces

In clinical pathology laboratories, the primary approach for detecting Cryptosporidium is still microscopic detection using stains, fluorescent antibodies (IFA), and other antigenic detection techniques. Microscopy is labor-intensive, requires a professional operator, and lacks sensitivity and specificity even though it just requires basic equipment and inexpensive consumables (Ryan *et al*., 2016b). Although microscopy is the "gold standard" for finding enteric parasites, advancements have been made over the past 15 years in

Table 4: Reports of Cryptosporidium infecting humans in different countries.

Sr. No.	Country	Types of Patients	Cryptosporidium species	Mostly Affected age	No. of infected persons (%)	References
1.	Kuwait (Jabryia)	Hospitalized patients	Not mentioned	Not mentioned	1/109 (0.9)	(Albert *et al*., 2016)
2.	China (Wuhan)	Children	*C. meleagridis*	2-5 year >5 year	4/238 (1.7) 1/53 (1.9)	(Wang *et al*., 2017)
3.	Saudi Arabia (Al-Taif)	Adults and children	Not mentioned	<5 year	14/163 (8.5)	(Hawash *et al*., 2017)
4.	Saudi Arabia (Makkah)	Children < 14 year	*C. hominis* and *C. parvum*	<5 year	23/1380 (1.7)	(El-Malky *et al*., 2018)
5.	Saudi Arabia (Riyadh)	In and out patients	*C. parvum*	0-10 year	6/5987 (0.1)	(Amer *et al*., 2018)
6.	Qatar (Doha)	Immigrants	*C. parvum* *C. meleagridis* *C. hominis*	23-29 year	38/839 (4.5)	(Boughattas *et al*., 2019)
7.	Thi–Qar Province (Al-Rifai)	Diarrheic patients	*C. parvum*	1-10 year 31-40 year	9/20 (45) 1/20 (5)	(Salim and Al-Aboody, 2019)
8.	Iraq (Al-kut)	Diarrheal (Both male and female)	*C. parvum* *C. hominis*	Not specified	38/96 (39.6) 4/96 (4.2)	(Alkhanaq and Al-Hadidi, 2022)

the development and validation of alternative diagnostic tests, such as the polymerase chain reaction (PCR) and immunofluorescence microscopy using labeled monoclonal antibodies, both of which have higher sensitivity than traditional microscopy. The testing of food samples has also been greatly aided by these techniques. However, evaluating samples of food presents various challenges (Iqbal *et al*., 2015b).

Because it is costly and time-consuming, immunomagnetic separation (IMS) is not frequently employed in diagnostic laboratories to identify Cryptosporidium oocysts in feces. IMS is nominated as an extra or alternative concentration step to separate Cryptosporidium oocyst (Ahmed and Karanis, 2018). The ability of various diagnostic procedures to identify Cryptosporidium in fecal samples from cattle, horses, and sheep was evaluated. These procedures included enzyme-linked immunosorbent assay (ELISA), microscopic (Kinyoun's staining), immunological (Direct Fluorescence Antibody tests or DFAT), and molecular methods (nested PCR). According to the findings, the sensitivity and specificity of each test are significantly influenced by the input samples; while Kinyoun's and DFAT proved to be reliable screening tools for cattle samples, DFAT and PCR analysis (targeted at the 18S rRNA gene fragment) were more sensitive for screening sheep and horse samples (Mirhashemi *et al*., 2015b).

A standard method to identify Cryptosporidium oocysts using IMS and IFA staining on lettuce and raspberries have been developed, with an overall sensitivity of 89.6 and 95.8%, and a specificity of 85.4 and 83.3%, respectively, for lettuce and raspberries. The use of IMS methods has significantly improved the specific detection of Cryptosporidium on food (Ryan *et al*., 2018b). Fecal inspection is the technique that is most frequently utilized to diagnose cryptosporidiosis in animals. According to the OIE's recommended procedure, a fecal smear is created and stained using customized Ziehl-Neelsen (mZN) staining. Comparing the fecal concentration method to a direct smear test, it was found to have a greater sensitivity for the detection of cryptosporidiosis (Shanmathi *et al*., 2020).

10. Control

Infected animals shed enormous quantities of oocysts which are infective and can survive for an extended period in moist and cool conditions as they are extremely environmentally stable. Infection can transfer through a variety of receptive hosts. Due to these reasons, cryptosporidiosis is a challenging disorder to control. Additionally, the oocysts are resistant to several disinfectants (Chlorine utilized in swimming pools, drinking water, and bleach based solid surface disinfectant) (Chalmers and Giles, 2010; Thomson, 2016). Waterborne transmission can be prevented by filtering or boiling drinking water. To collect the comparatively small oocysts while filtering, the pore size must be sufficiently small (Delahoy *et al*., 2018). Reverse osmosis and water filters with <1µm restriction are typically successful, however, they occasionally fail (Dillingham *et al*., 2002). Due to the oocysts' high chlorine tolerance, Cryptosporidium cannot be killed by using only chlorine water treatment (Delahoy *et al*., 2018).

11. Treatment

The best available treatments for cryptosporidiosis are paromomycin, azithromycin, roxithromycin, letrazuril, sinefungin, and nitazoxanide (Gorcea *et al*., 2020; Rossignol, 2010a). Rifaximin has antiparasitic properties as well. Other antimicrobial medications are also helpful in treating Cryptosporidium development. It involves medications such as rifabutin, rifaximin, roxithromycin, and clarithromycin (Florescu and Sandkovsky, 2016; Dhal *et al*., 2022a).

11.1. Medication for humans and animals

The first medication for treating cryptosporidiosis to be examined in humans was paromomycin (Rossignol, 2010b). Even though symptoms of cryptosporidiosis in immunocompetent individuals are typically self-limiting, paromomycin may be used as treatment therapy (Cacciò and Chalmers, 2016; Chavez and White Jr, 2018).

11.1.1. Nitazoxanide

Furthermore, Nitazoxanide has been authorized as a treatment strategy for children older than one year and immunocompetent individuals who have cryptosporidiosis (Cacciò and Chalmers, 2016; Chavez and White Jr, 2018). In immunocompromised adults, kids, and teenagers infected with cryptosporidiosis, nitazoxanide has demonstrated better effectiveness. Recently, there are two dosages of nitazoxanide: a 100mg/5ml oral solution and a 500mg tablet (Schneider *et al*., 2021).

11.1.2. Azithromycin (AZR)

A macrolide antibiotic called azithromycin (AZR) effectiveness against Cryptosporidium was examined in both animals and humans (Lee *et al*., 2017). For the treatment of pediatric cryptosporidiosis, azithromycin appeared to be superior to two anthelminthic medications. In certain individuals with reduced parasitic clearance and stool frequency, it also has been administrated in conjunction with paromomycin and nitazoxanide in compromised hosts (Sparks *et al*., 2015a).

11.1.3. Highly active antiretroviral therapy (HAART)

The prevalence of cryptosporidiosis among HIV-positive people has remarkably diminished due to the induction of HAART. This is brought on by an enhanced CD4 cell concentration which causes partial recovery of immunity. It also leads to the direct impact of protease inhibitors on the development and invasion of the parasite in the host cell. In developing countries, where cryptosporidiosis and HIV/AIDS poses to be threatened health issue tragically, it is not widely accessible because it is expensive (Cacciò and Chalmers, 2016; Sparks *et al*., 2015b).

11.1.4. Clofazimine (CFZ)

In vitro testing revealed that the lipophilic riminophenazine medication CFZ, which is accustomed to treat counteracting tuberculosis and leprosy is efficacious in the case of Cryptosporidium (Love *et al*., 2017). Notwithstanding, in the human trial, phase 2, it was considered to be inadequate in HIV patients who are highly immunocompromised (Iroh Tam *et al*., 2020), because of inefficient absorbance in individuals who were Crypto-infected with HIV (Dhal *et al*., 2022b).

11.1.5. Halofuginone

Halofuginone lactate is the only approved medication to treat cattle with chemotherapy for cryptosporidiosis in calf cases. Halofuginone lactate can lessen oocyst shedding and the length of diarrhea in calves, but it cannot entirely prevent or treat the condition (Bidaisee and Macpherson, 2014). In Europe, halofuginone is permitted for the treatment of calves (Lendner *et al*., 2015). By the early 1990s, it had been determined that coccidiostat halofuginone showed results for the treatment and prevention of cryptosporidiosis in calves (Brainard *et al*., 2021).

12. Zoonotic significance

The emergence of new foodborne parasites, which occur at the interface between animals, humans, and the environment has raised awareness of zoonoses worldwide. Despite the overall burden of parasitic diseases, the health status of people regarding foodborne parasite infections is still poorly understood. To fill in the knowledge gaps, it will be necessary to update data on parasite disorders (Bordier and Roger, 2013). Approximately, 60,400 deaths were declared to be caused by Cryptosporidium spp by the Global Enteric Multicenter Study (GEMS) in 2015 presenting 12.1% of deaths with diarrheal disease among children under age 5. It is the second most common cause of mild to severe diarrhea (5-15%) in newborns in Asian and Saharan African regions (Kotloff *et al*., 2013; Troeger *et al*., 2017). As part of the overall burden of disease, this measure will call for funding to be allocated for research, surveillance, and control initiatives that take foodborne parasite diseases into account. One-health approach is necessary to address the burden of foodborne parasites at the human-animal-environmental interface. One-health has improved the ability of authorities to reorganize and respond to the bulk of parasitic zoonosis by connecting zoonosis with agriculture and food safety (Bidaisee and Macpherson, 2014).

Conclusions: An infectious disease that is on the rise, cryptosporidiosis frequently causes diarrhea in both people and animals across the world. It can be contracted by consuming oocyst-contaminated food and water, and because it often resolves on its own in immunocompetent people, it can be misdiagnosed and underreported. The oocyst is extremely resistant to environmental and chemical risks, and because so many people are affected by waterborne epidemics and their related socioeconomic effects, their impact is rather substantial. Therefore, only preventative sanitary measures capable of preventing oocyst contamination of food and water might be used to control the illness. For the management and prevention of the disease in farm animals and humans, the role of veterinarians in the diagnosis, treatment, and counseling of cryptosporidiosis is vital.

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