



Cryptosporidium species and cryptosporidiosis in Japan: a literature review and insights into the role played by animals in its transmission

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ABSTRACT. *Cryptosporidium* species infect domestic animals, livestock, and humans. These protozoan parasites are frequently reported as major environmental contaminants in many countries despite their differing climatic, socioeconomic, and demographic factors. This review focuses on the research findings that relate to *Cryptosporidium* epidemiology, genetic diversity, and associated risk factors relating to animals, contaminated water sources, and humans in Japan. Adequate knowledge of these factors is essential for understanding the economic and public health importance of cryptosporidiosis in Japan so that effective control strategies against it are implemented. *Cryptosporidium* infections are highly prevalent in animals in Japan. Among the different animal species, cattle infections stand out because of their economic importance and zoonotic potential. Living circumstances in Japan restrain *Cryptosporidium* transmission between humans, but there is evidence to suggest that animals, especially those in close contact with humans, can be potential sources of human infections. Water sampling studies have provided clues about how environmental contamination with *Cryptosporidium* oocysts can cause infections in livestock and wild animals. There is some evidence of person-to-person transmission of cryptosporidiosis, but only occasionally and under certain circumstances. By identifying the major role played by animals in *Cryptosporidium* transmission to people in Japan, we highlight the urgent need for disease control against this pathogen.

KEY WORDS: animal, cryptosporidiosis, *Cryptosporidium*, human, Japan

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Cryptosporidiosis is considered an important cause of global morbidity and mortality, and concerns about it span both veterinary and public health areas [23, 24]; hence, it is included in the Neglected Diseases Initiative of the World Health Organization (WHO) [143]. *Cryptosporidium*, a ubiquitous parasite, has been recognized as one of the most important human diarrheal pathogens [81, 157]. The transmission cycles that exist for human infections include person-to-person transmission, zoonotic transmission, foodborne transmission, and waterborne transmission [29, 30, 49, 128, 168].

Of the many diagnostic techniques currently used to accurately assess parasite burdens, microscopy, copro-antigen detection (immunoassay, immunofluorescence assay, and immunochromatography tests), serological tests, and nucleic acid amplification methods are commonly used [24]. However, no gold-standard diagnostic tests or immunological tools are currently available for researchers to distinguish oocysts from different species [23]. Nevertheless, serologic assays based on antibody binding to *C. parvum* antigens can detect infections caused by various species and subtypes of this parasite [14, 22, 127]. Encouragingly, the advent of molecular technology is now revolutionizing our understating of the epidemiology (included speciation and subtyping), biology, and transmission of this parasite [29, 132, 170].

Although much progress has been made in *Cryptosporidium* research in Japan, no retrospective analyses have been done on the epidemiology and diversity of this parasite among humans or other animals in this country (or both). Although generally informative, a generalized review on *Cryptosporidium* infections in Asia lacked many aspects relating to the epidemiology, biology and transmission routes of this parasite [89]. This review aims to explore the current situation for cryptosporidiosis in Japan and to assess the potential risks it poses to human and animal populations, including information gathering about the environmental factors required to establish efficient control strategies against this parasitic disease.

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LITERATURE SEARCHING STRATEGY AND ELIGIBILITY CRITERIA

PubMed and Scopus databases were searched using only two key words: *Cryptosporidium* and Japan. There were no restrictions on year, language, host, or study type. The electronic journal platform for science and technology information in Japan (J-STAGE) was searched using the same criteria. The Google Scholar search engine was used to ensure the successful collection of data and the presence of full data for relevant papers where only abstracts were shown. Studies were considered eligible for inclusion if they had identified *Cryptosporidium*-positive samples within Japan. Any further molecular analyses and experimental studies on *Cryptosporidium* isolates from Japan were also included. No restrictions were added to the study population of interest (humans, animals, and environmental sources). Thus, studies that reported on *Cryptosporidium* in other countries were excluded. Studies that reported on pathogens causing diarrhea in Japan other than *Cryptosporidium* were excluded. Included were studies that reported on the relationship between *Cryptosporidium* and other pathogens. Included articles were also screened for additional local data. Time was not specified after retrieving the data from the different databases and all published papers until the year 2020 were permitted.

REPORTED ANIMAL CASES OF CRYPTOSPORIDIOSIS, SPECIES DIVERSITY AND PERSPECTIVES

Cattle

Epidemiology: Cryptosporidiosis in cattle in Japan was first reported in calves from Okayama, Miyagi, and Hokkaido prefectures [15, 61, 135, 139, 179] according to Kaneta and Nakai [71]. Earlier studies showed that *C. muris* or *C. muris*-like oocysts were present in cattle from Japanese slaughterhouses [82, 118] at infection rates of 4.7% in Miyagi [122], 3.9% in Kanagawa [79], 2.8% in Shizuoka [153], 1.2% in Fukushima [108], 1.2% in Saitama [119], and 3.4% in Tokushima Prefecture [156]. The aforementioned studies were mainly published locally and active surveillance was conducted after the year 2000. Major progress has been made in accurately detecting *Cryptosporidium* among dairy and beef cattle farms in many prefectures (Table 1). Different population sizes were investigated in these studies and the variable prevalence rates reflect the heterogeneity among the studies regarding animal age and the numbers of animals examined. However, although the data we retrieved were quite small in number, they support the notion that cryptosporidiosis is a major disease in the Japanese cattle population.

A significant correlation was found between *Fusobacterium* and *C. parvum* in cases of neonatal calf diarrhea in Okinawa, Kagoshima, Iwate and Hokkaido prefectures, suggesting that *Fusobacterium* may be an important aggravating factor for cryptosporidiosis in calves [52]. Regarding age, the assigned articles identified *C. parvum* as being the most prevalent species among pre-weaned calves that mainly had diarrhea, whereas *C. andersoni* was present in adults, as is similarly reported worldwide [32, 138].

Insufficient attention to the link between production losses and *Cryptosporidium* infections in the cattle industry seems likely. Because cattle livestock in Japan is estimated to include 50,100 beef farms (2,499,000 heads) and 16,400 dairy farms (1,323,000 heads) [149], a nationwide survey on cryptosporidiosis in these animals is worthwhile so as to estimate the disease burdens and the economic impacts on the cattle industry.

Cryptosporidium species and population genetics: As mentioned above, *C. muris* or *C. muris*-like oocysts from adult cattle were isolated in different prefectures [82, 118]. *Cryptosporidium andersoni* was initially misidentified as “*C. muris*” based on experimental infections in mice, although the species was detected in cattle at Miyagi Prefecture [71]. *Cryptosporidium* isolates were collected from a farm later on and the nucleotide sequences of 18S rDNA, heat-shock protein 70 (HSP70), and the oocyst wall protein (COWP) genes were compared with those from the *C. muris* RN66 isolate, and a novel type of *C. andersoni* (Kawatabi strain) was identified with the ability to infect SCID mice [140]. Similarly, isolates from the same prefecture were also proposed to be the same genotype and not *C. muris* [118], according to their 18s rRNA sequences. This unique genotype was reported in Hokkaido prefecture where it was suggested to be widespread in cattle [82, 97].

Knowledge about the *C. andersoni* Kawatabi strain is mainly based on the morphology of its oocysts, the sequences of its 18S rRNA and other genes, and its infectivity to mice, all of which make it dissimilar to *C. andersoni* isolates from cattle in other countries. This strain appears as the following two forms: type A (which is identical to the *C. andersoni* Kawatabi strain reported previously) and type B (a novel genotype, with a thymine nucleotide insertion in the 18S rRNA gene not present in type A), which has wide-spread transmission among cattle in Japan [55, 102, 115]. The infectivity of this strain has been studied in both immunocompetent and immunodeficient mouse models [100, 116], where knowledge about the minimum number of oocysts needed to reliably establish the infection was gained, thereby providing a mouse model for further investigations. However, one study reported that *C. andersoni* Kawatabi was not infective to normal and immunosuppressed *Cynomolgus* monkeys [96].

With its ability for zoonotic transmission and veterinary importance, *C. parvum* has gained prominence over *C. andersoni*. *Cryptosporidium parvum* was first reported to be present in Hyogo Prefecture, based on the morphology of its oocysts [133, 165]. Later, restriction fragment length polymorphism (PCR-RFLP) analysis of *Cryptosporidium* oocysts from cattle in Hokkaido revealed the presence of infections with *C. parvum* and *C. muris* [136]. *Cryptosporidium parvum* infections were confirmed in 14 naturally infected bovine animals from Hokkaido and Iwate prefectures by PCR-RFLP and sequence analysis [172]. Isolates from three naturally infected calves in Hokkaido and Gifu were characterized as the *C. parvum* IIa subtype [10].

Typing and subtyping analyses identified cattle from different prefectures as being infected with *C. parvum* (IIaA15G2R1), the dominant subtype infecting dairy cattle and humans in industrialized nations [34]. This subtype together with *Giardia intestinalis* assemblage E was shown to cause calf mortalities in Chiba Prefecture [104]. *Cryptosporidium bovis* and *C. ryanae* (previously known as a *Cryptosporidium* deer-like genotype [33]) were also reported in cattle from different prefectures.

Table 1. *Cryptosporidium* prevalence and species identification in cattle, Japan

Host	Region	Age range	No. tested	No. positive (%)	No. of species	<i>Cryptosporidium</i> genotypes and subtypes / remarks	Reference	
Cattle	Saitama	2–8 wk	3	1	1	<i>C. parvum</i> *. Numbers representing positive samples among two farms in the two prefectures	Miyagi <i>et al.</i> , 1990 [107]	
	Chiba		54	8 (14.8) ^{a)}	1	<i>C. muris</i> *	Suzuki <i>et al.</i> , 1998 [153]	
	Shizuoka	Adult	500	14 (2.8)	1	<i>C. muris</i> like oocysts* ¹⁾	Kaneta and Nakai 1998 [71]	
	Miyagi	Adult	512	24 (4.7)	1	<i>C. muris</i> (Kawatabi strain) ²⁾	Saeki <i>et al.</i> , 2000 [133]	
	Hyoogo	Variable	582	10 (1.7) ^{a)}	2	<i>C. muris</i> ; <i>C. parvum</i> *	Uga <i>et al.</i> , 2000 [165]	
	Hyoogo	D 1–30	30	28 (93) ^{a)}	1	<i>C. parvum</i> *	Satoh <i>et al.</i> , 2003 [140]	
	Miyagi	Adult	113	6 (5.3)	1	<i>C. andersoni</i> (Kawatabi strain) ²⁾	Sakai <i>et al.</i> , 2003 [136]	
		Calves	28	2 (7.1)	1		Matsubayashi <i>et al.</i> , 2004 [97]	
	Hokkaido	Tokachi	480	16 (3.33)	2	<i>C. parvum</i> ; <i>C. muris</i> by PCR-RFLP	Nakai <i>et al.</i> , 2004 [118]	
	Hokkaido	Shihoro	1; Molecular study	1	1	<i>C. andersoni</i> (Kawatabi strain) ²⁾	Koyama <i>et al.</i> , 2005 [82]	
	Miyagi	NS	516 beef cattle	21 (4)	1	<i>C. muris</i> like oocysts ¹⁾	Nagano <i>et al.</i> , 2007 [115]	
	Hokkaido	2–10 yr	325	5 (1.5) ^{a)}	1	<i>C. andersoni</i> (Kawatabi strain) ²⁾ Sampling was from a slaughterhouse in Hokkaido		
	Saga	2 yr	1; Molecular study	1	1	<i>C. andersoni</i> (Kawatabi strain type A, B) ²⁾ Sampling was done in Osaka Municipal Meat Inspection Center.		
	Honshu	17.1–37.4 mo	205	12 (5.9)	1	<i>C. andersoni</i> (Kawatabi strain type A, B) ²⁾ Sampling was done in Osaka Municipal Meat Inspection Center.	Matsubayashi <i>et al.</i> , 2008 [102]	
	Hokkaido							
	Shikoku							
	Kyushu							
	Miyagi	>24 mo	50	5 (10)	3	<i>C. parvum</i> (IIaA15G2R1); <i>C. andersoni</i> ; <i>C. deer</i> -like genotype	Amer <i>et al.</i> , 2009 [16]	
	Osaki							
	Hokkaido	Tokachi	80 diarrheic samples	60 (75)	2	<i>C. parvum</i> ; <i>C. bovis</i>	Karanis <i>et al.</i> , 2010 [72]	
	Miyagi	Osaki	2 mo–15 yr	113	23 (20)	2	<i>C. bovis</i> ; <i>C. ryanae</i>	Murakoshi <i>et al.</i> , 2012 [110]
	Tohoku	Adult	3,775 (slaughter house)	171 (4.5)	1	<i>C. andersoni</i> (Kawatabi strain type A, B) ²⁾	Ikarashi <i>et al.</i> , 2013 [55]	
			310 (the Kawatabi farm)	4 (1.3)				
	Hokkaido	Ishikari	107	25 (23) ^{a)}	3	<i>C. parvum</i> (IIaA15G2R1); <i>C. bovis</i> ; <i>C. ryanae</i>	Murakoshi <i>et al.</i> , 2013 [111]	
	Iwate	6–76 d	77	43 (56) ^{a)}	1	<i>C. parvum</i> (IIaA15G2R1)	Aita <i>et al.</i> , 2015 [12]	
	Kagoshima							
	Hokkaido	Tokachi	5–211 mo	94	2 (2.1)	1	<i>C. andersoni</i> (type A, B)	Aita <i>et al.</i> , 2015 [13]
	Okimawa	6–88 d	50 diarrheic	25 (50)	1	<i>C. parvum</i> (IIaA15G2R1)	Ichikawa-Seki <i>et al.</i> , 2015 [50]	
	Hokkaido	4–21 d	25 diarrheic	25 (100)				
	Hokkaido	calves	117	4 (3.4)	1	<i>C. parvum</i> (IIaA15G2R1)	Murakoshi <i>et al.</i> , 2016 [113]	
	Chiba	calves	4 diarrheic	3	1	<i>C. parvum</i> (IIaA15G2R1)	Matsuura <i>et al.</i> , 2017 [104]	
	Kyushu	3 mo–>12 mo	570 sera 33 cattle farms	549 (96.3)	1	Seropositive for <i>C. parvum</i> using Cpp23-ELISA	Masatani <i>et al.</i> , 2018 [94]	
	Iwate and Hokkaido	Variable	344 sera 9 cattle farms	258 (75)	1	Two farms suffered from <i>C. parvum</i> infections before (<i>C. parvum</i> -positive farms). The positive rates of antibodies against Cpp23 and CppGP15 in the <i>C. parvum</i> -positive farms was 63.0% (n=133/211). In contrast, 18.8% were positive for the <i>C. parvum</i> -negative farms (n=25/133).	Ichikawa-Seki <i>et al.</i> , 2019 [51]	

a) Some positive samples were from diarrheic animals. *Species that may be considered disputable because they were only morphologically identified. 1) It has been proposed that *C. andersoni* (Kawatabi strain) is the correct genotype, not *C. muris*. 2) The *C. andersoni* Kawatabi strains confirmed in these studies are based on their 18S rRNA gene sequences and other genes, and their infectivity to mice. *C.*, *Cryptosporidium*; d, day old; wk, week; mo, month; yr, year; NS, not stated.

Table 2. *Cryptosporidium* prevalence and species identification in pigs, Japan

Host	Region	Age range	No. tested	No. positive (%)	No. of species	<i>Cryptosporidium</i> genotypes and subtypes / remarks	Reference			
Pigs	Kanagawa	1–3 mo	232 weaned piglets	77 (33.2)	1	<i>C. parvum</i> * utilizing immunofluorescent staining of oocysts.	Izumiyama <i>et al.</i> , 2001 [68]			
		6 mo	252 fattening porkers	1 (0.4)						
	Saitama	60 d	4 underdeveloped	2	2	<i>C. parvum</i> pig genotype II or <i>C. suis</i> . PCR-RFLP analysis.	Yui <i>et al.</i> , 2010 [182]			
		35–60 d	40 penmates	30 (75)						
		<1 mo	39 Pre-weaned	7 (17.9)	NS			Utilizing immunofluorescent staining of oocysts. Totally; out of 334 examined pigs, 79 were infected (23.7%).	Yui <i>et al.</i> 2014 [183]	
		1–<2 mo	29 Weaned	8 (27.6)						
		2–6 mo	190 finished	62 (32.6)						
		Sows, Sow candidates	76	2 (2.6)						
			<1 mo	55 Pre-weaned	15 (27.3)			2	<i>C. suis</i> ; <i>C. scrofarum</i> Totally; out of 344 examined pigs, 112 were infected (32.6%).	Yui <i>et al.</i> 2014 [184]
			1–2 mo	65 Weaned	31 (47.7)					
	2–6 mo		172 finished	59 (34.3)						
	sows		36	4 (11.1)						
	boars		16	3 (18.8)						

*Species proposed by morphology only and may therefore be questionable. C., *Cryptosporidium*, d, day old; mo, month; NS, not stated.

Cryptosporidium parvum, *C. andersoni*, *C. bovis* and *C. ryanae* are the major species infecting cattle world-wide [33, 138]. Among them, *C. parvum* is the most pathogenic species in both cattle and humans [123], whereas *C. andersoni* and *C. bovis* seem to have caused only a few human cases [132]. The epidemiological and genotyping findings testify the zoonotic importance of *C. parvum* while highlighting the economic losses caused by cryptosporidial infections in the Japanese cattle farming industry. Effective control strategies merit consideration as do careful animal management by farm workers and visitors.

Pigs

Relatively few studies have focused on *Cryptosporidium* infections in pigs in Japan. No *Cryptosporidium* oocysts were detected among examined adult pigs in slaughterhouses in Saitama [119], Fukushima [108], Miyagi [118, 122] and Hokkaido [82]. *Cryptosporidium* infections had a low prevalence among pigs in Aichi prefecture (1.9%) [159]. Nevertheless, four epidemiological studies investigating *Cryptosporidium* infections in pigs from Kanagawa and Saitama prefectures (Table 2) were conducted. In Saitama prefecture, *Cryptosporidium* infections were associated with diarrhea in pigs, whereas the isolates obtained from pigs in Kanagawa Prefecture may have contained a mixture of both *C. suis* and *C. scrofarum* because the oocysts from these species are morphologically similar to *C. parvum* oocysts [68, 184]. Recently, *C. suis* and *C. scrofarum* (previously called pig genotype II [87]) were reported in pigs from Saitama prefecture [182, 184].

Altogether, 4,670 pig farms (9,346,000 heads) were estimated to be present in Japan in a 2017 study [149]. Because previous studies focused on adults, *Cryptosporidium* infections in piglets remain unknown. The findings from previous studies suggest a high prevalence of *Cryptosporidium* infections occur mainly in piglets and young pigs in Japan. *Cryptosporidium suis* and *C. scrofarum* are the main species identified in pigs worldwide, and a few human cases have been reported [29, 132]. Other studies have reported on *C. parvum* occurring occasionally in pigs from other countries [132]. Cryptosporidiosis in pigs is usually subclinical in nature but is sometimes associated with non-hemorrhagic diarrhea [74, 144]. However, piglets experimentally infected with *C. parvum* derived from calves developed moderate to severe mucosal attenuation with lymphoid hyperplasia and severe gastrointestinal disorders [28, 126]. *Cryptosporidium parvum* was identified as a major species infecting cattle and humans, and was also identified in different water samples in Japan. Clearly, further studies are required to estimate the true prevalence and species composition of *Cryptosporidium* infections among piglets and young pigs from different prefectures, to elucidate the transmission dynamics of *C. parvum* among animals in Japan and the zoonotic importance of any species infecting the pigs.

Dogs and cats

Pet animals, especially dogs and cats, share close relationships with humans and act as reservoirs of zoonotic pathogens, including *Cryptosporidium* spp. [25, 26]. *Cryptosporidium* infections in cats in Japan that were reported on in early studies showed low prevalence rates in Osaka (38.5%; [58]) and Hyogo Prefectures (3.9%; [164]) [19]. Large-scale surveys were conducted in different prefectures coupled with molecular tools, which enabled the wide spread of *C. canis* (previously the dog genotype [31]) and *C. felis* among dogs and cats, respectively, in Japan to be determined (Table 3). This finding may have a zoonotic implication [29, 88, 131, 171]. A raccoon dog had a *Cryptosporidium* infection, the isolate of which was identified as a new *C. parvum* subtype [10, 99, 101].

Rodents and rabbits

Different *Cryptosporidium* species and genotypes have been identified in rodents in Japan (Table 4). Early studies identified *Cryptosporidium* oocysts in 14.8% of the brown rats captured in Osaka City [59] and 21.3% of the brown rats captured in the cities of Osaka, Tokyo, and Chiba [76, 106]. The oocysts were assumed to be *C. parvum* or *C. muris* based on their morphologies, which

Table 3. *Cryptosporidium* prevalence and species identification in dogs and cats, Japan

Host	Region	Age range	No. tested	No. positive (%)	No. of species	<i>Cryptosporidium</i> genotypes and subtypes/remarks	Reference
Dogs	Niigata	9 wk	Molecular study	1	1	<i>C. parvum</i> dog genotype	Abe <i>et al.</i> 2002 [6]
	Osaka	adult	140 stray dogs	13 (9.3)	1	<i>C. canis</i>	Abe <i>et al.</i> 2002 [7]
	Tochigi	NS	772	1	NS	Samples were collected in 1979, 1991 and 2001	Asano <i>et al.</i> , 2004 [20]
	Osaka	4 yr	1	1	1	<i>C. canis</i> mixed with <i>Giardia</i> infection PCR-RFLP analysis	Matsubayashi <i>et al.</i> 2004 [98]
	Miyagi	NS	294	1 (0.3)	1	<i>C. canis</i>	Satoh <i>et al.</i> 2006 [142]
	NS	1 mo–16 yr	190 household dogs	12 (6.3)	NS	Coproantigen detection using commercial ELISA kit	Itoh <i>et al.</i> 2008 [64]
	Saitama	Juvenile, adult	906	8 (0.9)	1	<i>C. canis</i>	Yamamoto <i>et al.</i> , 2009 [174]
	Osaka	3 mo–15 yr	77	3 (3.9)	1	<i>C. canis</i>	Yoshiuchi <i>et al.</i> 2010 [181]
	Hokkaido	2 mo–18 yr	529 household dogs	38 (7.2)	1	<i>C. canis</i>	Itoh <i>et al.</i> 2014 [65]
	Tohoku	≤3 mo	471 pet shop puppies	149 (31.6)			
	Kanto		98 veterinary nursing school dogs				
	Kinki	2–11 yr		18 (18.4)			
	Kyushu						
	Okinawa						
Miyagi Niigata Gunma Shizuoka Aichi	2 mo–11 yr	314 breeding kennel dogs	66 (21)	1	<i>C. canis</i>	Itoh <i>et al.</i> 2019 [66]	
Osaka	NS	1 raccoon dog*	1	1	<i>C. parvum</i> cattle genotype This study was conducted at Osaka Municipal Tennoji Zoological Gardens	Matsubayashi <i>et al.</i> 2004, 2005 [99, 101]	
Cats	Tokyo metropolitan	Variable	608	23 (3.8)	NS	One year survey from February, 1988 to February, 1989	Arai <i>et al.</i> 1990 [19]
	Chiba	NS	326	1	NS	Sampling from December 1998 to December 1999	Hata <i>et al.</i> , 2000 [45]
	NS	1 mo–17 yr	89 household cats	9 (10.1)	NS	Coproantigen detection using commercial ELISA kit	Itoh <i>et al.</i> 2008 [64]
	Saitama	Juvenile, adult	1,079	30 (2.8)	1	<i>C. felis</i>	Yamamoto <i>et al.</i> , 2009 [174]
	Osaka	3 mo–15 yr	55	7 (12.7)	1	<i>C. felis</i>	Yoshiuchi <i>et al.</i> 2010 [181]
	Nagano Saitama Aichi Gifu Miyagi	1 mo– 12 yr	286	4 (1.4)	1	<i>C. felis</i>	Ito <i>et al.</i> 2016 [62]
	Hokkaido	1 mo–23 yr	357 household cats	7 (2.0)	1	<i>C. felis</i>	Ito <i>et al.</i> 2017 [63]
	Tohoku	1–3 mo	329 pet shop kittens	1 (0.3)			
	Kanto						
	Kinki						
Kyushu							
Okinawa							

*284 fecal samples were collected from various zoo animals and a raccoon dog was the only *Cryptosporidium*-positive animal. *C.*, *Cryptosporidium*; wk, week old; mo, month; yr, year; NS, not stated.

may be incorrect taxonomically [76].

In the study by Nakai *et al.* [118], *C. muris* was reported in field mice captured from the pastures of a cattle farm in Miyagi prefecture and, interestingly, this isolate was genetically distinct from the *C. andersoni* Kawatabi strain identified from cattle on this farm. Additionally, a Japanese field mouse (Kawatabi) genotype was proposed to be a novel, genetically distinct (18s rRNA gene) *C. muris* genotype that differs from the *C. muris* and *C. andersoni* Kawatabi strains; hence, the authors named it “*C. muris*”

Table 4. *Cryptosporidium* prevalence and species identification in rodents and rabbits, Japan

Host	Region	Age range	No. tested	No. positive (%)	No. of species	<i>Cryptosporidium</i> genotypes and subtypes/remarks	Reference
Rats	Tokyo	NS	231 house rats	32 (13.9)	NS	<i>Rattus norvegicus</i> ; <i>Rattus rattus</i> and other species were investigated	Yamaura <i>et al.</i> , 1990 [175]
	Hyogo Nishinomiya	NS	50 (<i>Rattus norvegicus</i>)	19 (38)	3	<i>C. meleagridis</i> ; <i>C. parvum</i> ; and unknown genotypes.	Kimura <i>et al.</i> 2007 [76]
Mice (<i>Apodemus speciosus</i>)	Miyagi	NS	25	2	1	<i>C. muris</i>	Nakai <i>et al.</i> , 2004 [118]
	Kawatabi farm	NS	25	2 (8)	1	<i>C. muris</i> novel genotype (Kawatabi genotype)	Hikosaka and Nakai 2005 [47]
	Miyagi Osaki	NS	15	4 (26.6)	2	<i>C. ubiquitum</i> ; <i>C. muris</i> (Kawatabi genotype) and novel genotype (Naruko genotype)	Murakoshi <i>et al.</i> 2013 [112]
Chinchillas (<i>Chinchilla lanigera</i>)	Examined at Banquet animal Hospital, Tokyo	-	13 juveniles 45 juvenile and adult 5 adults	13 0 0	1	<i>C. ubiquitum</i> (XIId). Eight of the cases were fatal. All the 13 positive cases were imported from the Czech Republic, while 50 negatives were from Netherlands and USA	Kubota <i>et al.</i> 2019 [83]
Rabbits	Kanagawa	Juvenile	66 (diarrheic)	13 (19.7)	2	Two types identified based on microscopic examination. All juveniles were died after diarrhea	Shibashi <i>et al.</i> , 2006 [145]
		Adult	30 (healthy)	1 (3.3)			

C., *Cryptosporidium*; NS, not stated.

Japanese field mouse genotype” [47]. Adding another complication, a recent study identified not only *C. ubiquitum* and *C. muris* (Kawatabi genotype) in field mice, but also a novel genotype the authors named the “Naruko genotype” [112]. Interestingly, all of these studies were conducted in Miyagi prefecture, and together with the reports of *Cryptosporidium* in cattle, this raises concerns about the species and genotypes circulating in this area beside the cycles of transmission between different hosts and its zoonotic importance. Clearly, more studies are required to clarify these issues, and multilocus genotyping (sequencing) besides other biological and infection models in mice, will be useful for this.

Cryptosporidium species are incriminated in the morbidity and mortality of pet rodents and rabbits. *Cryptosporidium ubiquitum* (XIId) in chinchillas was reportedly associated with a high fatality rate [83]. Similarly, juvenile pet rabbits with diarrhea that died were microscopically identified as having *Cryptosporidium* infections in Kanagawa Prefecture [145]. The reports included in this section reflect the highly diverse *Cryptosporidium* population structure in Japan, and the complexity of the transmission cycles.

Birds

A few cases of cryptosporidiosis have been reported in birds in Japan (Table 5). *Cryptosporidium* infections in chicken were first reported in 11 flocks on six Japanese poultry farms [60]. Elsewhere, an isolate was assayed for infectivity to turkeys, quails and other experimental animals [36, 37]. The oocyst sizes were estimated in another study to be somewhere between the sizes of *C. baileyi* and *C. meleagridis* oocysts [103]. This isolate was later molecularly characterized as *C. baileyi* [75]. To our knowledge, only three studies have been conducted on cryptosporidiosis in poultry in Japan, and the estimated number of farms was 2,440 for layers and 2,310 for broilers [149]. The causative agents of high morbidity and mortality on a large Japanese quail farm in Chiba Prefecture turned out to be mixed infections of *Cryptosporidium* with *Mycoplasma gallisepticum* [109].

Many genotypes have been isolated from other birds investigated for *Cryptosporidium* (Table 5); they include *C. meleagridis*, *C. baileyi*, *C. galli*, avian genotype III, new avian genotype V (*C. avium*), and a novel genotype. Among them, *C. meleagridis*, *C. baileyi* and *C. galli* are well known and cause high morbidity and mortality [130]. *Cryptosporidium meleagridis* is the third most common *Cryptosporidium* spp. in humans worldwide [130, 169], and may be linked with human infections in Japan. The zoonotic species, *C. meleagridis*, was identified in a pet cockatiel that shared close contact with humans. Little is known about the pathogenicity of many avian genotypes, but *Cryptosporidium* avian genotype III causes chronic vomiting in peach-faced lovebirds (*Agapornis roseicollis*) [90]. Interestingly, *Cryptosporidium* avian genotype V was first reported in Japanese cockatiels [4] and *C. avium* was the proposed species later [48]. Lastly, Makino *et al.* [91] reported the case of a 1-month-old brown wood owlet with severe dehydration and anorexia following a week of vomiting and severe diarrhea attributed to a mixed infection with *C. avium* and a novel genotype.

Reptiles and wild animals

While wild animals contribute to environmental contamination [18, 128] with *Cryptosporidium*, pet reptiles may directly contribute to human infections with this parasite. Little is known about cryptosporidiosis in wildlife and reptiles in Japan (Table 6), but among the reported species, horse and skunk genotypes and *C. parvum* and *C. meleagridis* are human pathogens, whereas other species have not been reported in humans [185]. This constitutes a public health risk via direct contact or contamination of water sources with infective oocysts, but further information is needed to clarify the role of wild animals in environmental contamination,

Table 5. *Cryptosporidium* prevalence and species identification in birds, Japan

Host	Region	Age range	No. tested	No. positive (%)	No. of species	<i>Cryptosporidium</i> genotypes and subtypes / remarks	Reference
Psittacine and passerine birds	Imported and local birds	NS	534	5	NS	Histopathological observation	Tsai <i>et al.</i> , 1992 [158]
Ferrets	Kanazawa	NS	3	3	1	Ferret genotype of <i>C. parvum</i>	Abe and Iseki, 2003 [2]
Cockatiels	Kanazawa	NS	2	2	2	<i>C. meleagridis</i> and <i>C. baileyi</i>	Abe and Iseki, 2004 [3]
	Kanagawa	NS	4	4	3	<i>C. meleagridis</i> , avian genotype III, and a new avian genotype V.	Abe and Makino 2010 [4]
Peach-Faced Lovebirds (<i>Agapornis roseicollis</i>)	Yokohama Bird Clinic	3mo–16 yr	37	100	1	<i>C. avian</i> genotype III Twenty birds showed clinical, gastrointestinal signs. Birds were purchased at pet shops in Kanagawa prefecture	Makino <i>et al.</i> , 2010 [90]
Owls	Obihiro Zoo	7-wk NS	3 snowy owls 17 different spp.	1 0	1 -	<i>C. baileyi</i> -	Nakagun <i>et al.</i> 2017 [117]
Wood Owls	Kanagawa	1 mo	1 brown wood owl	1	2	Mixed <i>C. avium</i> and novel genotype	Makino <i>et al.</i> 2018 [91]
	Fujisawa Avian Clinic	NS	19 different spp.	1	1	Same novel genotype in 3 mo spotted wood owl	
Psittaciformes	Tokyo	NS	153	10 (6.5)	2	Avian genotype III; <i>C. galli</i>	Iijima <i>et al.</i> 2018 [54]
Passeriformes	Chiba		90	13 (14.4)	2	<i>C. galli</i> ; <i>C. baileyi</i>	
Galliformes	Saitama Gunma		22	1 (4.5)	1	<i>C. baileyi</i>	
Ostriches	Aomori	Chicks	20 with diarrhea and mortalities	Only 1 case examined	1	<i>C. parvum</i> ¹⁾ in immunohistochemically stained sections	Ueki <i>et al.</i> , 2001 [163]
Japanese quails	Chiba	NS	17	7 (41.2)	NS	Histopathological observation. <i>Cryptosporidium</i> mixed infections with <i>M. gallisepticum</i> in 7 out of 17 diseased quail from a herd with a conjunctivitis and sinusitis.	Murakami <i>et al.</i> , 2002 [109]
Chickens	NS	31 to 86 d	68 layers 12 broilers	25 4 (36.2)	1	<i>C. baileyi</i> * Totally 29/80 positive cases Histological diagnosis and electron microscopy.	Itakura <i>et al.</i> , 1984 [60], Kimura <i>et al.</i> , 2004* [75]
	NS	4–6 wk	200 growing layer	10 (5)	NS	Retrospective histologic examinations were carried out on the bursae of Fabricius collected in 1977 and 1978	Iwabuchi and Kirioka, 1992 [67]
	Hyogo	≤49–≥80 d	418 77 farms	37 (8.9) 14 farms	1	<i>C. baileyi</i> ¹⁾ Fecal and histological examinations	Genta <i>et al.</i> , 2001 [38]
Migratory ducks (<i>Anseriformes</i>)	Hokkaido Tokachi	NS	200	23 (11.5)		<i>C. avian</i> genotype III and <i>C. baileyi</i>	Salama <i>et al.</i> , 2020 [137]

*Isolates were reexamined by molecular methods at a later date. 1) Proposed species name may be disputable because only morphological characterization was conducted. C., *Cryptosporidium*; d, day old; wk, week; mo, month; yr, year; NS, not stated.

especially of water sources.

CRYPTOSPORIDIUM CONTAMINATION OF JAPANESE WATER SOURCES

Water contamination by *Cryptosporidium* oocysts is a major source of cryptosporidiosis in humans [128, 129, 148]. There have been three large-scale cryptosporidiosis outbreaks in Japan [27]. Water contamination caused an outbreak of cryptosporidiosis in 1996 in Ogose town, Saitama Prefecture, where approximately 9,140 people were infected and which was attributed to non-complete removal of *Cryptosporidium* oocysts in the source water during the water treatment process [151, 173]. Tap water samples from different sites, raw-water samples from the water treatment plant, and effluent samples treated by the wastewater treatment plants all contained oocysts during this outbreak [173]. It was assumed that small wastewater treatment plants located upstream of the water source possibly worsened this outbreak [151].

Another report of a water-borne cryptosporidiosis outbreak was in a building in Hiratsuka, Kanagawa Prefecture, at the end of the summer of 1994 [85]. *Cryptosporidium* oocysts were found in tap water and other water samples from a receiving tank and wastewater pits, the cause of which was attributed to sanitary sewage contamination of the drinking water [85]. A nationwide survey of water source supplies throughout Japan in 1997, which was conducted by the Ministry of Health and Welfare, reported

Table 6. *Cryptosporidium* prevalence and species identification in reptiles and wild animals, Japan

Cosmo4877 host	Region	Age range	No. tested	No. positive (%)	No. of species	<i>Cryptosporidium</i> genotypes and subtypes/remarks	Reference
Banded Mongoose <i>Mungos mungo</i>	Osaka	NS	Molecular study	1	1	New genotype, closely related to that of bears. <i>Mungos mungo</i> was brought from Tanzania to the Osaka Municipal Tennoji Zoological Gardens	Abe <i>et al.</i> , 2004 [8]
Snakes	Different regions	NS	469	57 (12.1)	1	<i>C. snake</i> genotype W11	Kuroki <i>et al.</i> 2008 [86]
Hedgehog	Examined at Banquet animal	NS	1	1	1	<i>C. horse</i> genotype (VIbA13)	Abe and Matsubara 2015 [5]
Snakes	Hospital, Tokyo		2	2	2	<i>C. varanii</i> ; <i>C. serpentis</i> snake genotype	
Lizards			5	5	2	<i>C. varanii</i> ; <i>C. serpentis</i> lizard genotype	
Spiny-tailed lizards	Tokyo Saitama	NS	Case study	2	1	<i>C. avium</i> (novel variant)	Kubota <i>et al.</i> , 2020 [84]
Sika deer	Hokkaido Hidaka, Ishikari, Nemuro	Fawns, yearlings and adults	319	25 (7.8)	1	<i>C. deer</i> genotype	Kato <i>et al.</i> 2016 [73]
	Nine prefectures	NS	271	18 (6.6)	4	<i>C. ryanae</i> , <i>C. bovis</i> , <i>C. sp. deer</i> genotype; <i>C. meleagridis</i>	Yamazaki <i>et al.</i> , 2018 [177]
	Hokkaido Tokachi	1–≤5 yr or Unknown	137	13 (7.5)	1	<i>C. deer</i> genotype	Shirozu <i>et al.</i> , 2020 [147]
Raccoons (<i>Procyon lotor</i>)	Osaka	Adult Young <6 mo	116	7 (6.03)	2	<i>C. skunk</i> genotype (subtype XVIa) and <i>C. parvum</i>	Hattori <i>et al.</i> 2018 [46]
Bats (<i>Eptesicus nilssonii</i>)	Hokkaido Tokachi	NS	3	2	1	<i>C. bat</i> genotype XII	Murakoshi <i>et al.</i> 2018 [114]

C., *Cryptosporidium*; mo, month; yr, year. NS not stated.

that *Cryptosporidium* oocysts were identified in 8 (2.9%) of the 277 examined sites in 94 rivers [125, 166].

Water samples collected from rivers, water purification plants, wastewater treatment plants and sewage samples were contaminated with *Cryptosporidium* oocysts in different Japanese areas (Table 7). Interestingly, the *C. parvum* identified by PCR-RFLP from the Obihiro River in Hokkaido was viable and infective to SCID mice, and the pattern of oocyst shedding was similar to that of the inoculated control isolates [162]. An outbreak of cryptosporidiosis, which was attributed to contaminated swimming pools, was reported in a hotel in Nagano Prefecture where many sports participants during swimming training developed diarrhea and other intestinal symptoms [155, 178]. Ten swimming pools belonging to a sports center in Chiba Prefecture were used by the returning participants from this joint training event, and four of the pools were investigated for the presence of *Cryptosporidium* oocysts and two of them tested positive [53].

The species identified from different water samples across prefectures and rivers to date are *C. parvum*, *C. meleagridis*, *C. hominis*, *C. andersoni*, *C. suis*, a snake genotype, pig genotypes, and two new genotypes (Table 7). The wide range of species and genotypes is supported by some studies that show a strong correlation between livestock raising and water contamination [69, 124]. Thus, it can be concluded that livestock and wild animals play key roles in *Cryptosporidium* transmission, as well as in environmental contamination.

Guidelines for controlling *Cryptosporidium* contamination of drinking water were adopted in Japan [105], and the water quality monitors used in water purification plants are assayed to confirm successful *Cryptosporidium* control [80]. An annual *Cryptosporidium* infection risk of approximately 10^{-4} or below was estimated for the reuse of treated wastewater during a 2-year survey from two Japanese wastewater treatment plants, suggesting that it is possible to meet the target infection risk [154].

HUMAN CASES OF CRYPTOSPORIDIOSIS

A variety of transmission cycles are related to *Cryptosporidium* in nature; they include food, water, pets, and domestic and wildlife animals, and do not require any interaction between them [49]. Three major outbreaks of cryptosporidiosis occurred in Ogose town (Saitama Prefecture), in Hiratsuka (Kanagawa Prefecture), and in Awaji (Hyogo Prefecture) [27, 85, 173, 176] where a large number of cases with severe diarrhea and acute gastrointestinal illness were reported. Another outbreak occurred in a contaminated swimming pool in a hotel in Nagano Prefecture [53, 155, 178] and a foodborne outbreak was reported in Japan [180]. Other reported cases of cryptosporidiosis in patients examined in Japanese hospitals are included in Table 8.

The first case of *C. meleagridis* was identified from naturally infected human together with both *C. hominis* and *C. parvum*

Table 7. *Cryptosporidium* prevalence and species identification in environmental samples, Japan

Region	No. tested/type of samples	No. positive (%)	No. of species	Remarks and species/genotypes identified	Reference
Kanagawa	16 water samples surveyed in 1996	13 (81)	NS	9 (75%) of 12 sites examined in 1996 was contaminated.	Hashimoto and Hirata 1998 [41]
	10 water samples surveyed in 1997	7 (70)		4 (67%) of the 6 sites examined in 1997 was contaminated.	
Kanagawa	Sagami river and its tributaries			Larger number of oocysts was detected in tributaries of the Sagami river where many stock raising farms are located. Sampling was done at August and December 1998, 1999 and August 2000.	Izumiyama <i>et al.</i> , 2001 [69]
	16 Sagami River water samples	12 (63.2)	NS		
Hyogo	3 Sakawa River water samples	9 (69)	1	<i>C. parvum</i> (bovine genotype) was detected by PCR-RFLP.	Ono <i>et al.</i> 2001 [124]
	69 points samples in the 13 rivers	38 (55)		Strong correlation between the numbers of raised cattle and rivers contamination. Sampling was from July to October in 1999.	
Hyogo	18 rivers	13 (72)	2	<i>C. parvum</i> (human and bovine genotypes) was detected by PCR-RFLP. Samples were collected in 1998 and 1999.	Ono <i>et al.</i> 2001 [125]
	Of which 156 water samples collected	74 (47)			
Nationwide survey	73 raw wastewaters	7 (10)	NS	67 wastewater treatment plants were sampled and IFAT was used for detection in 1996.	Suwa and Suzuki 2001 [150]
	74 reclaimed wastewaters	9 (12)		Water samples were taken from major rivers in the Kanto area which are important water sources for Tokyo and surrounding cities during 1996 and 1997.	
	48 Tone, Edo and Tama rivers samples	3 (6)			
	20 Ara river samples	3 (15)			
	20 Oppo river samples	1 (5)			
Hokkaido	10 rivers	6	1	IFAT-DIF kit was used for <i>C. parvum</i> * detection. Samples were collected in August, September and November 1999.	Tsushima <i>et al.</i> 2001 [160]
	Of which 28 surface water samples	14 (50)			
Kanagawa	13 samples of 50 l river source water	13 (100)	NS	A water purification plant was used and sampling was carried out from July 1998 to September 1999.	Hashimoto <i>et al.</i> 2001, 2002 [42, 43]
	26 samples of 2,000 l-filtered water	9 (35)			
Hyogo	11 livestock slaughterhouse waste water	6 (55)	NS	<i>Cryptosporidium</i> oocysts were detected after waste water treatment in 4 (36) and 5 (45) of livestock and poultry slaughterhouses respectively. Sampling was from August to December 1999.	Saeki <i>et al.</i> , 2002 [134]
	11 poultry slaughterhouse waste water	7 (64)			
Hokkaido Tokachi	Three rivers were samples	NS	1	<i>C. parvum</i> * using IFAT and DAPI staining. One-year survey from August 1999 to October 2001 with maximum number of oocysts during late summer to early autumn.	Tsushima <i>et al.</i> 2003 [161]
	7 Sewage samples	NS	3	<i>C. parvum</i> ; <i>C. meleagridis</i> ; <i>C. sp.</i> Pig genotype were identified. Sampling was twice a month, from May to August 2003 at a sewage treatment plant.	
Tokyo metropolitan area	16 water samples	11 (69)	7	<i>C. hominis</i> , <i>C. parvum</i> , <i>C. andersoni</i> , Snake genotype (<i>C. sp.</i> 938), <i>C. sp.</i> pig genotype II (PGI-26), and two new genotypes. Sampling was from August to November 2004.	Masago <i>et al.</i> , 2005, 2006 [92, 93]
	Koyama river			Using Quenched probe PCR (QProbe PCR) to quantify the 18S rRNA gene and denaturing gradient gel electrophoresis (DGGE) followed by DNA sequencing.	
Tributary rivers of the Tone river	23 water samples	21 (91)	4	<i>C. sus</i> , <i>C. andersoni</i> , <i>C. pig</i> genotype II and <i>C. meleagridis</i> . Sampling was from October 2007 to February 2008.	Haramoto <i>et al.</i> 2008 [39]
	22 surface water samples	7	NS	Using a reverse transcription loop-mediated isothermal amplification assay RT-LAMP for detection of <i>Cryptosporidium</i> .	
Miyagi	9 ground water samples	0			Inomata <i>et al.</i> , 2009 [56]
	14 river water samples	11 (78.6)	NS	Reverse transcription-loop-mediated isothermal amplification assay (RT-LAMP) was used for detection.	
Variable regions	26 Hog farm drainage effluent and its downstream river water	20 (76.9)	NS	Results representing samples examined using improved RT-LAMP with the highest detection sensitivity.	Inomata <i>et al.</i> , 2011 [57]
	50 Surface water	12 (24)			
	27 Finished water, spring water, shallow well water and river-bed water	0			
Hokkaido	64 surface water samples	26 (41)	NS	Samples were collected from 16 drinking water treatment plants in July and December 2008 and 2009.	Haramoto <i>et al.</i> 2012 [40]
Tokyo metropolitan area	14 water samples	12	NS	Samples were collected from tributary rivers of the Tone river basin from November to December 2009. <i>Cryptosporidium</i> were detected and quantified using alternately binding probe competitive PCR (ABC-PCR); Real-time PCR and microscopy	Kishida <i>et al.</i> , 2012 [78]

*Proposed species designation is questionable. *C.*, *Cryptosporidium*; NS, not stated.

Table 8. Reported cases of human cryptosporidiosis in Japan

Region	No. of gastroenteritis patients	No. examined	No. positive (%)	No. of species	Remarks and species / genotypes identified	Reference
Kochi Medical School	1 112	1 0	1 0	NS NS	A 5-year-old boy with nephrotic syndrome during the period from June to July, 1985	Suzuki <i>et al.</i> , 1986 [152]
Tokyo Metropolitan Komagome Hospital	2	2	2	1	A middle-age homosexual male with AIDS and a 31-year-old female; <i>C. parvum</i> HNJ-1 (IIaA15G2R1)	Masuda <i>et al.</i> , 1991 [95] Amer <i>et al.</i> , 2010 [17]
Kyoto Prefectural University of Medicine	Case report	1	1	NS	A 24-year-old Japanese male with severe prolonged watery diarrhea after returning from India	Shiota <i>et al.</i> , 1994 [146]
Kanagawa Hiratsuka	461	25	12 (48)	1	461 patients with cholera-like symptoms among the staff members and customers who visited one of the 10 public houses or a dancing school in a building in Hiratsuka, Kanagawa, at the end of summer in 1994. <i>C. parvum</i> *	Kuroki <i>et al.</i> , 1996 [85]
Saitama Medical School	34	28 children 6 family members	10 (36)	1	<i>C. parvum</i> *, during Saitama, Ogose water outbreak of cryptosporidiosis in 1996	Yamazaki <i>et al.</i> , 1997 [176]
Saitama Institute of Public Health	8,812 citizens 274 visitors 54 employees out of the town	522	125 (23.9)	NS	During Saitama, Ogose water outbreak of cryptosporidiosis in 1996	Yamamoto <i>et al.</i> , 2000 [173]
Saitama Tokyo Osaka Kanagawa Hokkaido Iwate Overseas	Molecular study	-	22	3	<i>C. meleagridis</i> ; <i>C. hominis</i> and <i>C. parvum</i> . Isolates were from naturally infected 22 human (Immunodeficient and unknown status patients) including cases from Ogose outbreak in 1996	Yagita <i>et al.</i> , 2001 [172]
Mizonokuchi Hospital, Kanagawa	Case report	1	1	1	<i>C. parvum</i> *, 28-year-old Japanese homosexual man having AIDS	Fujikawa <i>et al.</i> , 2002 [35]
Different hospitals Hyogo, Awaji	4,273 129	4,273 -	3 126 ¹⁾	NS NS	During 5 years (1996–2000) survey High school students and the teaching staff who went to Hokkaido on a school excursion complained of severe diarrhea, in 2002	Obana <i>et al.</i> , 2002 [120] Endo and Izumiya 2004 [27]
Osaka	Case report	1	1	1	Mixed <i>Giardia</i> and <i>C. parvum</i> human genotype* in a 25-year-old Japanese male with persistent watery diarrhea, after returning from India	Abe <i>et al.</i> , 2005 [9]
Nagano	151 ^{a)} 273 ^{b)} 288 ^{c)}	31 - 86	30 - 74	1 - -	<i>C. parvum</i> human genotype* ¹⁾ . Outbreak in swimming pool in the hotel in Nagano Prefecture	Yokoi <i>et al.</i> , 2005 [178] Ichinohe <i>et al.</i> , 2005 [53] Takagi <i>et al.</i> , 2008 [155]
Chiba	48	6	2	NS	Outbreak due to contaminated swimming pools belonging to the sports center in Chiba prefecture used by the returning participants from the Nagano joint training outbreak	Ichinohe <i>et al.</i> , 2005 [53]
Tokyo Osaka	Molecular study	-	5	2	<i>C. hominis</i> (Ic, Ia, Ib) and <i>C. parvum</i> (Iic and Iia)	Abe <i>et al.</i> , 2006 [10]
Ehime	19	19	3	1	<i>C. meleagridis</i> . Outbreak among high school students in August 2006	Asano <i>et al.</i> , 2006 [21]
Osaka, Sakai	4	4	3	1	<i>C. parvum</i> Iia; food born outbreak in company workers due to raw meat dish called “Yukke: Korean-style beef tartar” and raw liver at a roisserie, 2006	Yoshida <i>et al.</i> , 2007 [180]
JSDF Hospital Kure, Hiroshima NS	Case report Molecular study	1 -	1 3 isolates	NS 1	A 23-year-old Japanese military man Five new <i>C. meleagridis</i> genotypes One HIV-positive and two HIV-negative adults	Ogata <i>et al.</i> , 2009 [121] Abe 2010 [1]
IMSUT Hospital of Tokyo University Tokushima University Hospital	Case report Case report	1 1	1 1	NS 1	A 33-year-old man with human immunodeficiency virus (HIV) <i>C. meleagridis</i> ; 63-year female with persistent diarrhea in Japan after allogeneic cord blood transplantation	Adachi <i>et al.</i> , 2016 [11] Kagawa <i>et al.</i> , 2018 [70]

*Proposed species designation is questionable. 1) Case numbers were reported following assigned criteria including that they had either laboratory confirmed cryptosporidiosis or watery diarrhea (clinical cryptosporidiosis). a, b, c) Cases numbers of patients with symptoms reported by three different studies: a, Yokoi *et al.*, 2005 [53] and c, Takagi *et al.*, 2008 [155]; b, Ichinohe *et al.*, 2005 [53] and c, Takagi *et al.*, 2008 [155]; c, *Cryptosporidium*; NS, not stated.

(previously human genotype I and bovine genotype II, respectively, [23]) from different geographic areas based on analysis by PCR-RFLP and 18s rRNA sequencing [172]. A gastroenteritis outbreak from *C. meleagridis* (PCR-sequenced 18s rRNA) was reported among high school students from a dormitory in Ehime [21]. Five new *C. meleagridis* genotypes from humans in Japan (3 isolates, one HIV-positive and 2 HIV-negative) were reported, as based on the sequence analysis of multiple genes that differ genetically from other isolates in other countries [1]. Quite recently, another *C. meleagridis* infection case was identified [70].

Cryptosporidium parvum HNJ-1, the cryptosporidial reference strain in Japan, was first isolated from an infected woman [95]. Further molecular studies characterized this isolate using multilocus sequencing including, 18s rRNA [6], thrombospondin-related adhesive protein (TRAPC1, TRAP-C2), HSP70, COWP, beta-tubulin, alpha-tubulin, polythreonine-region, elongation factor 1 alpha (EF-1 α) [141], transcribed ribosomal region (ITS rRNA), dihydrofolate reductase, and surface glycoprotein 60 genes [17]. This isolate, which was subtyped as IIaA15G2R1, contains extensive polymorphism in the ITS region, as compared with other *C. parvum* isolates. Five other isolates have come from Japanese patients in Tokyo and Osaka who were infected with *C. hominis* (Ie, Ia, Ib) and *C. parvum* (IIc and IIa in HNJ-1 isolate) [10]. Furthermore, *C. parvum* IIa also caused a foodborne disease outbreak in 2006 [180]. *Cryptosporidium parvum* infections have been detected in cattle, rats and raccoons from different prefectures, while rats, cockatiels and sika deer were reported to be infected with *C. meleagridis*. These findings are indicative of zoonotic transmission as well as environmental contamination.

Person to person is another possible transmission route for human infections in Japan after people are exposed to contaminated swimming pools, contaminated food, or contaminated drinking water. However, living conditions in Japan, particularly the good hygienic measures and health services, along with advances in wastewater treatment should decrease the risk of direct transmission of cryptosporidiosis between humans. Previous recordings of disease were correlated with accidental outbreaks. Moreover, evidence of person-to-person transmission from overseas travelers exists for *C. parvum*, *C. meleagridis* and *C. hominis*, which were recorded in foreign travelers to Japan from different countries (India, Indonesia, and Kenya) [172].

Contrastingly, two molecular studies reported the infection with *C. hominis* among Japanese patients from different geographical area including patients linked to Ogose outbreak in 1996 as well as overseas travelers [10, 172]. Furthermore, it was identified as the cause of outbreak due to contaminated swimming pool in the hotel in Nagano Prefecture [178]. The histories of the samples used in these studies are unclear and while there is no evidence of infections with *C. hominis* in animals in Japan, *C. hominis* oocysts were identified in water samples from the Koyama river and rivers in Hyogo Prefecture [92, 93, 125]. *Cryptosporidium hominis* infects a wide range of livestock species and non-human primates other than humans and water-borne transmission is probably the route of transmission [167]. Consequently, this important species may be transmitted by person-to-person contact or by contaminated water sources. Therefore, the health authorities in Japan are encouraged to conduct nationwide molecular screening for *Cryptosporidium* among humans with gastrointestinal symptoms who visit hospitals.

CONCLUDING REMARKS

This review highlights the very high genetic diversity of *Cryptosporidium* species circling among animals and humans in Japan. Many zoonotic species of *Cryptosporidium* were reported in animals, suggesting the potential risk to the Japanese population. Our review also highlights the high morbidity and mortality of cryptosporidiosis across different animal species and its consequential economic impacts. Little is known about *Cryptosporidium* infection in cattle in Japan and continuous monitoring is strongly recommended in order to properly understand its economic and zoonotic impact. The situation of *Cryptosporidium* infection in the pig and poultry sectors is largely unknown and regional prefectural surveillances are required. Prompt surveillance systems by prefectural governments (Livestock Hygiene Service Centers) tasked with disseminating, analyzing, and publishing the resultant data will be valuable for establishing control strategies. Continuous improvement and maintenance of high-quality standards relating to transmission control against this pathogen are essential, particularly for water sources, to reduce the risk of zoonotic infections.

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