Public health and ecological significance of rodents in Cryptosporidium infections

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ABSTRACT

Cryptosporidium is one of the most important genera of intestinal zoonotic pathogens that cause diarrhea in both humans and animals. Rodents are common and important hosts or carriers of pathogens with public health importance, and rodents play an important role in the ecology of zoonotic transmission. The overall worldwide prevalence of Cryptosporidium spp. in rodents is 19.8% (4589/23142). Twenty-five known Cryptosporidium species and 43 genotypes have been identified, and C. parvum is the dominant species in rodents worldwide. Rodents transfer pathogens to humans by the direct route or by serving as intermediate hosts transmitting the pathogens to other animals. We review the epidemiology, diversity, and transmission routes of Cryptosporidium spp. in rodents. The main purpose of this review is to highlight Cryptosporidium infection in rodents and its transmission, associated risk factors, and prevention; in addition, we assess the public health and ecological significance of Cryptosporidium infections from the One Health perspective.

1. Introduction

Cryptosporidium spp. are foodborne and waterborne parasites with zoonotic potential. The parasites cause watery diarrhea in both humans and animals (domestic animals, mammals, rodents, birds, fish, marsupials, reptiles, and amphibians). Drinking source water, coastal water, recreational use water, wastewater, and market vegetables have been found to contain Cryptosporidium spp. in field investigations \cite{1,5,9,11,12}. At least 44 valid Cryptosporidium species and approximately 120 genotypes have been described to date. Cryptosporidiosis is a global parasitic disease that usually presents as self-limiting diarrhea, abdominal pain, low-grade fever, nausea, vomiting, and weight loss \cite{1,5}. The condition can be fatal in immunosuppressed individuals (e.g., persons infected with HIV/AIDS) \cite{1}. The current treatment for cryptosporidiosis, nitazoxanide (NTZ), has only moderate clinical efficacy, and no vaccines are available \cite{1,5}.

The life cycle of Cryptosporidium involves several developmental stages (schizogamy, gametogenesis, and spor stages). The oocysts are ingested by susceptible hosts through contaminated food or water, after which they invade the epithelial cells lining the gastrointestinal gland mucosa and replicate intracellularly \cite{11,53}. Fresh oocysts are excreted from the host with the feces and can cause infections in other susceptible hosts by contaminating food or water \cite{11,12,53}. The rigid spore wall may play a vital role in the survival of the parasite in hostile environments, thus being responsible for large waterborne as well as foodborne outbreaks of the disease \cite{4,53,92-94}.

Rodents are an abundant and diversified order of mammals \cite{92,99}. Since the Middle Ages, it has been recognized that rodents can contribute to human disease \cite{9,11,98,99}. In modern times, rodents are also recognized as carriers of many pathogens with public health importance. Almost 10% of the global rodent population is either a carrier or reservoir of pathogens with public health importance \cite{11,98}. Rodents have high population densities and live close to the ground, so they are frequently infected with Cryptosporidium spp. While much progress has been made in Cryptosporidium research, no retrospective analyses have been done on the epidemiology, diversity, or transmission routes of this parasite in rodents. This review aims to explore the current situation for cryptosporidiosis in rodents and to assess the potential risks posed to human and animal populations.

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2. Molecular characteristics of Cryptosporidium in rodents

2.1. Prevalence of Cryptosporidium in rodents

To date, Cryptosporidium infection in rodents has been documented in 19 countries, with the prevalence ranging from 0.7% to 100%. The overall average infection rate is 19.8% (4589/23142). Regarding the geographical distribution, the prevalence across different regions ranges from 2.2% to 28.0%. Europe has a higher prevalence (28.0%) (1860/6638) than other documented regions. The overall prevalence values in Asia, North America, South America, Africa, and Oceania are 18.6% (1394/7510), 15.2% (1265/8299), 7.3% (11/150), 2.2% (3/135), and 13.7% (56/410), respectively (Table 1).

It is difficult to explain the discrepancies in the prevalence of Cryptosporidium spp. among studies because prevalence is affected by many factors, including the host species composition, host species gender, host species age, season, the geographical distribution of the sample population, the sample size, and the ecological conditions. However, according to current data, the major rodent species vary among regions; the prevalence of Cryptosporidium and the major Cryptosporidium species in different species of rodents are also different, and the types of rodents studied may influenced the differences in prevalence (Table 3, Supplementary Table S1). However, the reported prevalence of Cryptosporidium in Africa and Oceania is possibly related to the relative lack of research data.

2.2. Cryptosporidium species distributions in rodents

To date, 25 known Cryptosporidium species (C. parvum, C. hominis, C. muris, C. tyzzeri, C. andersoni, C. meleagridis, C. suis, C. dierichi, C. apodemi, C. scrofarum, C. alticola, C. microti, C. myocastoris, C. ubiquitum, C. occultus, C. homai, C. wrairi, C. varanii, C. erinacei, C. canis, C. viatorum, C. proliferans, C. rubeyi, C. ratti, and C. ryanae) and 43 genotypes (rat genotype II-V, bamboo rat genotype I-III, mouse genotype II, muskrat genotype I-II, skunk genotype, hamster genotype, ferret genotype, chipmunk genotype I-V, vole genotype I-VII, apodemus genotype I-II, muskrat genotype I-II, squirrel genotypes I-III, deer mouse genotype I-IV, Cryptosporidium sp. 1, Cryptosporidium sp. 2, Naruko genotype, Qinghai vole genotype, C. muris novel genotype, and the C. environment isolate) have been identified in rodents (Table 2).

Cryptosporidium species and dominant distributions differ by region. In Asia, 19 species and 15 genotypes have been identified; C. parvum is the dominant species. In Europe, 15 species and 16 genotypes have been identified, and C. parvum is the dominant species. In North America, three species and four genotypes have been identified, and C. parvum is the dominant species. In South America, only C. parvum has been detected. In Africa, two species and one genotype have been identified, and C. andersoni is the dominant species. In Oceania, four species and five genotypes have been identified, and C. homai is the dominant species (Fig. 1). The species and genotypes of Cryptosporidium infecting rodents in Asia and Europe are very diverse; this may be due to the comparatively large number of studies and the species richness of rodents studied. C. parvum has been shown to be common in rodents throughout the world; the species is similarly prevalent in humans and cattle.

2.3. Cryptosporidium in rodent types

Cryptosporidium infections have been documented 54 rodent species. According to the descriptions of the environment of the sample collection sites and details concerning rodents’ living habits listed in 86 epidemiological articles, the types of rodents can be divided into wild, domestic pet, farm, and laboratory animals. The overall prevalence rates in wild, pet, farm, and laboratory animals are 20.5% (3848/18804), 27.0% (373/1381), 14.5% (354/2439), and 2.7% (14/518), respectively (Table 1).

Table 1

| Location     | Asia | China | Positive/total samples (%) | Zoonotic Cryptosporidium spp. Positive no. |
|--------------|------|-------|---------------------------|-------------------------------------------|
| Europe       | Poland | 50.3% (863/1715) | C. parvum (687); C. ubiquitum (1) |
| Finland      | 0.7% (2/272) | – | – |
| Czech Republic | 15.5% (219/1409) | C. parvum (3); C. muris (4); C. dierichi (21); C. andersoni (4); C. ubiquitum (1); C. occultus (3) |
| Slovak Republic | 19.4% (97/499) | C. parvum (15); C. muris (1); C. dierichi (5); C. suis (4); C. scrofarum (28); C. hominis (2); C. ubiquitum (4) |
| Spain        | 25.1% (156/621) | C. parvum (108); C. muris (18); C. meleagridis (1); C. tyzzeri (2) |
| Italy        | 27.7% (36/130) | C. parvum (263); C. muris (73) |
| England      | 27.0% (427/1580) | Chipmunk genotype I (2) |
| Unkonw       | 14.6% (69/412) | C. parvum (2); C. muris (2); C. dierichi (22) |
| Subtotal     | 28.0% (1860/6638) | C. parvum (1078); C. muris (98); C. meleagridis (1); C. tyzzeri (48); C. dierichi (48); C. andersoni (4); C. suis (4); C. scrofarum (28); C. hominis (2); C. ubiquitum (6); C. occultus (3); Chipmunk genotype I (2) |
| North America | 15.2% (1265/8299) | C. parvum (510); C. ubiquitum (19); Muskrat genotype I (24); Muskrat genotype II (6); Skunk genotype (4) |
| Brazil       | 2.2% (135/6100) | C. parvum (8) |

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Table 1 (continued)

| Factors | Positive/total samples (%) | Zoonotic Cryptosporidium spp. Positive no. |
|---------|-----------------------------|----------------------------------------|
| South America Kenya | 7.3% (11/150) | – |
| Nigeria | 100% (1/1) | – |
| Subtotal | 2.2% (3/138) | C. andersoni (1) |
| Subtotal | 13.2% (51/385) | C. tyzzeri (6); C. vuitarum (3) |
| Oceania New Zealand | 20.0% (5/25) | – |
| Australia | 13.2% (51/385) | C. tyzzeri (6); C. vuitarum (3) |
| Rodent type Wild | 20.9% (3848/18804) | C. parvum (1617); C. muris (145); C. meleagridis (3); C. tyzzeri (66); C. diictrich (48); C. andersoni (3); C. suis (10); C. scrofa (32); C. hominis (22); C. ubiquium (37); C. occulta (7); C. erinacei (1); C. canis (1); C. vuitarum (39); Muskrat genotype I (24); Muskrat genotype II (6); Skunk genotype (4); Chipmunk genotype I (10) |
| Farm | 14.5% (354/2439) | C. parvum (169); C. muris (10); C. ubiquium (85); C. occulta (4) |
| Pet | 27.0% (373/1381) | C. parvum (15); C. muris (11); C. andersoni (42); C. ubiquium (50) |
| Lab | 2.7% (14/518) | C. muris (1); C. tyzzeri (1); C. andersoni (2); C. ubiquium (1) |
| Total | 19.8% (4589/23142) | C. parvum (1801); C. muris (167); C. meleagridis (3); C. tyzzeri (67); C. diictrich (48); C. andersoni (47); C. suis (10); C. scrofa (32); C. hominis (22); C. ubiquium (173); C. occulta (11); C. erinacei (1); C. canis (1); C. vuitarum (39); Muskrat genotype I (24); Muskrat genotype II (6); Skunk genotype (4); Chipmunk genotype I (10) |

Note: “–” indicates no Zoonotic Cryptosporidium spp.

3. Public health of zoonotic Cryptosporidium spp

3.1. Zoonotic Cryptosporidium spp. in humans

3.1.1. C. hominis

Although humans are the major host species for C. hominis, the species has been reported in a number of wildlife hosts, including rodents. To date, C. hominis has only been detected in wild striped field mice (Apodemus agrarius) in Slovakia [64,87]. Subtyping of C. hominis at the gp60 locus identified nine subtype families (Ia to Ij); only the subtype IbA10G2 of C. hominis has been reported in wild striped field mice [64]. The subtype IbA10G2 of C. hominis has been identified in humans, cattle, marsupials, and the European hedgehog. This is the main subtype associated with outbreaks of cryptosporidiosis caused by C. hominis [64]. Although the source of C. hominis in wild rodents is unclear, these animals can clearly serve as potential reservoirs for this pathogen.

3.1.2. C. parvum

C. parvum is one of the two most common Cryptosporidium species causing human cryptosporidiosis. The parasite infects a broad range of hosts, including various bovids, cameldids, equids, canids, non-human primates, and marine mammals [94]. C. parvum is the dominant species in rodents; at least 20 species of rodents such as rats, mice, voles, squirrels, Rhizomys sinensis, and Chinchilla lanigera are known to be positive for C. parvum [8,11,24,28,37,44,64,80,87]. C. parvum has been detected in wild rodents, pet rodents, and farm rodents in 14 countries [37,80,87,24,64]. Pet rodents and farm rodents have close contact with humans. Therefore, pet rodents and farm rodents are potential reservoirs of C. parvum and thus may play an important role in the ecology of the zoonosis.

Subtyping of C. parvum at the gp60 locus identified more than 20 subtype families. Several studies that identified C. parvum in rodents have conducted typing at the gp60 locus; a variety of C. parvum subtypes including IaA15G2R, IaA16G2R1, IaA17G2R1, IaA18G1R1b, IaA18G3R1, IldA15G1, IldA10, IldA9, IldA6, IlbA15G1, and IlbA13G1 have been reported from rodents [37,80,87,24,64]. The Ila, Ild, Ili, and Ilb subtypes were previously reported in humans [87]. C. parvum Ilp is genetically related to the Ild and Ilb subtypes; they have a broad host range and the potential for human infection. Rodents are frequently infected with IldA15G1, and the most prevalent subtype family Ild in rodents is also commonly found in cattle and other livestock.

3.1.3. C. meleagridis

C. meleagridis is a common cause of cryptosporidiosis in avian hosts. This species is the third most common species involved in human cryptosporidiosis [38,80]. To date, only four cases of C. meleagridis have been reported in wild rodents. Japan, USA, Spain, and Malaysia have reported the presence of C. meleagridis in R. norvegicus, Peromyscus spp., Rattus rattus, and in one unidentified wild rodent species. These findings may indicate a possible role of rodents in the mechanical transmission of this pathogen [38,65,80].

3.1.4. C. vuitarum

C. vuitarum has been frequently identified in human and urban wastewater; however, there were no reports in any animal species other than humans prior to recent studies reporting its occurrence in wild rodents [52,66,91]. Rodent species include Edward’s long-tailed rat (55.3%; 2138) and wild rats (12.0%; 25228) in China and swamp rats in (14.3%; 3/21) in Australia [52,66,91]. To date, nine subtypes of C. vuitarum (XVaA3a–XVaA3g, XVaA6, and XVB2A1G) have been identified globally. Subtypes XVbA2G1, XVaA6, XVaA3g, XVaA3h, XVC2A1G, XVC2A1G1, XVC2A2G1h, and XVdA3 have been found in rodents. Interestingly, subtypes XVaA3a to XVaA3f were identified only in humans. XVaA6 was isolated from wastewater, and thus the presence of the XVa subtype family in rodents suggests that wild rats may have the potential for zoonotic transmission and must be considered a potential
Table 2

Recognized Cryptosporidium spp. in the rodents.

| Species name | Type host(s) | Major host(s) | Reports in humans          | Reports in rodents Positive no. | gp60 | Reference |
|--------------|--------------|---------------|-----------------------------|---------------------------------|------|-----------|
| C. hominis*  | Human (*Homo sapiens*) | Humans | Most common reported        | Rattus norvegicus (1); Rattus ratus (1); Mus musculus (69); Apodemus flavicollis (70); Clethrionomys glareolus (442); Microtus othus (423); Apodemus sylvaticus (132); Mus spretus (1); Peromyscus sp. (165); Microtus pennsylvanicus (13); A. agrarius (13); Ondatra zibethicus (8); Sperrimophilus beecheyi (149); Sciurus carolinensis (6); Tamiasciurus hudsonicus (9); Tamias striatus (38); Marmota monax (2); Castor canadensis (2); Castor fiber (16); Erethizon dorsatum (2); Hydrochoerus hydrochaeris (8); Cavia porcellus (1); Chinchilla lanigera (3); Phodopus sungorus (4); Musculus corpus (1); Rattus norvegicus (13); Rattus tanezumi (3); Marmota flaviventris (33); Wild rat (13); Qinghai vole (3) | IbA10G2 | [64,67] |
| C. parvum*   | Cattle (*Bos taurus*) | Ruminants; humans | Second most common reported | R. norvegicus (1); R. rattus (1); Wild rat (1) | – | [5,37,80,87,24,64] |

C. meleagridis

Turkey (*Meleagris gallopavo*)

Birds, humans

Commonly reported

Commonly reported

R. norvegicus (1); R. rattus (1); Wild rat (1); Syrian flying squirrel (1); M. spretus (1); Rattus norvegicus (158); Rattus tanezumi (3); Marmota flaviventris (33); Wild rat (13); Qinghai vole (3) | – | [38,65] |

C. ubiquitum

Cattle (*B. taurus*)

Ruminants, rodents, primates

Commonly reported

Commonly reported

R. norvegicus (1); C. lanigera (49); Chinese flying squirrel (1); M. spretus (5); Callosciurus erythraeus (19); Wild rat (10); Laboratory rats (1); Qinghai vole (1) | XiHa; XiId; XiIi | [5,11,40,42,43,46] |

C. viatorum

Human (*Homo sapiens*)

Rodents

Many reported

Qinghai vole (1); Lepomys edwardsi (11); Swamp rats (3); Wild rats (25) | XVbA2G1; XVcA3g; XVaA3b; XVcA2G1a; XVcA2G1b; XVbA3 | [52,66,91] |

C. muris

House mouse (*Mus musculus*)

Rodents

Commonly reported

R. norvegicus (4); R. rattus (14); M. musculus (61); A. flavicollis (3); C. glareolus (2); M. spretus (5); A. agrarius (13); Ondatra zibethicus (8); Sperrimophilus beecheyi (149); Sciurus carolinensis (6); Tamiasciurus hudsonicus (9); Tamias striatus (38); Marmota monax (2); Castor canadensis (2); Castor fiber (16); Erethizon dorsatum (2); Hydrochoerus hydrochaeris (8); Cavia porcellus (1); Chinchilla lanigera (3); Phodopus sungorus (4); Musculus corpus (1); Rattus norvegicus (13); Rattus tanezumi (3); Marmota flaviventris (33); Wild rat (13); Qinghai vole (3) | – | [7,8,20,27,52,59,63,87] |

C. canis

Dog (*Canis familiaris*)

Dogs

Commonly reported

R. norvegicus (1); M. musculus (51); A. agrarius (13); Ondatra zibethicus (8); Musculus corpus (1); Rattus norvegicus (4); R. tanezumi (1); P. sungorus (40) | IXa; IXb; IXc | [89] |

C. tyzzeri

Mouse (*Mus musculus*)

Rodents

Some reported

Some reported

R. norvegicus (1); M. musculus (51); A. agrarius (13); Ondatra zibethicus (8); Musculus corpus (1); Rattus norvegicus (4); R. tanezumi (1); P. sungorus (40) | – | [5,37,75] |

C. andersoni

Cattle (*B. taurus*)

Cattle

Some reported

Some reported

R. norvegicus (4); M. monax (1); P. sungorus (40) | – | [40,47,70,76] |

C. erinacei

European hedgehog (*Erinaceus europaeus*)

Hedgehogs, horses

Some reported

Some reported

R. tanezumi (1) | – | [87] |

C. suis

Pig (*Sus scrofa*)

Pig

Some reported

Some reported

A. flavicollis (4); Microtus brandti (–) | – | [37,64] |

C. daricii

Yellow-necked mouse (*Apodemus flavicollis*)

Rodents

Two reported

Two reported

A. flavicollis (43); A. sylvaticus (4); A. agrarius (2) | – | [40,47,70,76] |

C. occultus

Brown rat (*Rattus norvegicus*)

Rodents

Two reported

Two reported

R. norvegicus (5); R. sibiricus (4); R. tanezumi (1); Wild rats (5) | – | [5,46,49,50,52,49] |

C. scrofarum

Pig (*S. scrofa*)

Pig

One reported

One reported

A. flavicollis (5); M. arvalis (4); A. agrarius (19) | – | [61,87] |

C. ryanae

Cattle (*B. taurus*)

Cattle

None reported

None reported

R. norvegicus (1) | – | [13] |

C. wrairi

Guinea pig (*Cavia porcellus*)

Rodents

None reported

None reported

C. porcellus (159); C. erythraeus (1) | – | [40,45,71,82] |

C. homai

Guinea pig (*Cavia porcellus*)

Rodents

None reported

None reported

C. porcellus (39) | – | [40,82] |

C. apodemi

Striped field mouse (*A. agrarius*)

Rodents

None reported

None reported

A. flavicollis (11); A. agrarius (12); A. sylvaticus (2) | – | [37,64] |

C. alticolis

Common vole (*M. arvalis*)

Rodents

None reported

None reported

M. arvalis (7) | – | [35] |

C. microti

Common vole (*M. arvalis*)

Rodents

None reported

None reported

M. arvalis (46); A. flavicollis (2) | – | [35,37] |

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| Species name       | Type host(s)          | Major host(s)       | Reports in humans | Reports in rodents Positive no. | gp60 | Reference         |
|-------------------|-----------------------|---------------------|-------------------|---------------------------------|------|-------------------|
| *C. myocastor*    | Nutria (Myocastor *cyopus*) | Rodents             | None reported     | *M. coypus* (5)                 | –    | [42]              |
| *C. proliferans* | East African mole rat (Tachyoryctes *splendens*) | Rodents             | None reported     | Tachyoryctes *splendens* (–)    | –    | [46]              |
| *C. variegatus*   | numerous reptiles    | Reptiles            | None reported     | *C. lanigera* (–)               | –    | [53]              |
| *C. rufus*        | Spermophilus          | Rodents             | None reported     | *C. erythraeus* (2); *Spermophilus* ground squirrel (–) | –    | [55,57]          |
| *C. ratti*        | Brown rats (*Rattus norvegicus*) | Rodents             | None reported     | *R. norvegicus* (37); *R. rattus* (1) | –    | [4]               |
| *C. striatus*     | Peromyscus spp.      | Rodents             | Many reported     | Sciurus *vulgaris* (2); Wild rat (8) | –    | [32,40,44,47,48,76] |
| *C. variegatus*   | Mephitis mephitis    | Fox, human          | Many reported     | *C. erythraeus* (4)             | –    | [77]              |
| *C. variegatus*   | *O. zibethicus*      | Rodents             | One reported      | *O. zibethicus* (24)            | –    | [29,54]          |
| *C. variegatus*   | *O. zibethicus*      | Rodents             | One reported      | *O. zibethicus* (6); *Microtus brandti* (–) | –    | [29,54]          |
| *C. variegatus*   | *R. rattus*          | Rodents             | None reported     | *R. norvegicus* (35); *R. rattus* (24); *Microtus brandti* (8); *Muridae* (2); Wild rats (6) | –    | [29,43,45]      |
| *C. variegatus*   | *R. norvegicus*      | Rodents             | None reported     | *R. norvegicus* (5)             | –    | [29,43,45]      |
| *C. variegatus*   | *R. sinensis*        | Rodents             | None reported     | *R. sinensis* (54)              | –    | [49,50]          |
| *C. variegatus*   | *R. sinensis*        | Rodents             | None reported     | *R. sinensis* (1)               | –    | [49,50]          |
| *C. variegatus*   | *R. sinensis*        | Rodents             | None reported     | *R. sinensis* (5)               | –    | [49,50]          |
| *C. variegatus*   | *T. striatus*        | Rodents             | None reported     | *T. striatus* (28)              | –    | [50,54]          |
| *C. variegatus*   | *T. striatus*        | Rodents             | None reported     | *T. striatus* (5); *T. striatus* (1) | –    | [50,54]          |
| *C. variegatus*   | *Eutamias sibiricus* | Rodents             | None reported     | *T. striatus* (–)               | –    | [50,54]          |
| *C. variegatus*   | *T. striatus*        | Rodents             | None reported     | *T. striatus* (1); *C. lanigera* (1) | –    | [50,54]          |
| *C. variegatus*   | *M. domesticus*      | Rodents             | None reported     | *M. domesticus* (11)            | –    | [47,77]          |
| *C. variegatus*   | *O. zibethicus*      | Rodents             | None reported     | *M. arvalis* (1); *O. zibethicus* (24) | –    | [29,54]          |
| *C. variegatus*   | *O. zibethicus*      | Rodents             | None reported     | *Microtus brandti* (–); *O. zibethicus* (6) | –    | [29,54]          |
| *C. variegatus*   | *M. arvalis*         | Rodents             | None reported     | Meadow vole (1)                 | –    | [35]             |
| *C. variegatus*   | *M. arvalis*         | Rodents             | None reported     | *M. arvalis* (1)                | –    | [35]             |
| *C. variegatus*   | *M. arvalis*         | Rodents             | None reported     | *M. arvalis* (1)                | –    | [35]             |
| *C. variegatus*   | *M. arvalis*         | Rodents             | None reported     | *M. arvalis* (3)                | –    | [35]             |
| *C. variegatus*   | *M. arvalis*         | Rodents             | None reported     | *M. arvalis* (2)                | –    | [35]             |
| *C. variegatus*   | *M. arvalis*         | Rodents             | None reported     | *M. arvalis* (1)                | –    | [35]             |
| *C. variegatus*   | *M. arvalis*         | Rodents             | None reported     | *M. arvalis* (6)                | –    | [35]             |
| *Apodemus*        | *Apodemus* spp.      | Rodents             | None reported     | *A. flavicollis* (8)            | –    | [58]             |
| *Apodemus*        | *Apodemus* spp.      | Rodents; water      | None reported     | *A. flavicollis* (4); *A. agrarius* (5) | –    | [37]             |
| *S. beecheyi*     | *S. beecheyi*        | Sciuridae spp.      | None reported     | *C. erythraeus* (2)             | –    | [77]             |
| *S. beecheyi*     | *S. beecheyi*        | Sciuridae spp.      | None reported     | *C. erythraeus* (1)             | –    | [77]             |

(continued on next page)
3.1.5. C. ubiquitum was restricted to the house mouse subspecies; subtype IXb with hosts, each type having different natural host specificities [75]. gp60

Snakes, and horses, among others [94]. Subtyping of potential, but novel subtype XIIi has unknown human infective potential.

Species name Type host(s) Major host(s) Reports in humans Reports in rodents Positive no. gp60 Reference

| Species name | Type host(s) | Major host(s) | Reports in humans | Reports in rodents | Positive no. | gp60 | Reference |
|--------------|--------------|---------------|-------------------|-------------------|--------------|------|-----------|
| Cryptosporidium sp. 1 | environmental sample; water | – | None reported | – | – | [38] |
| Cryptosporidium sp. 2 | – | – | None reported | M. musculus (1) | – | [5] |
| Qinghai vole genotype | Microtus fuscus Vole | None reported | Qinghai vole (3) | – | [89] |
| Novel genotype of Brandt’s vole | Brandt’s vole Vole | None reported | Brandt vole (–) | – | [54] |
| Novel genotype | Apodemus spp. Vole | None reported | Wild rat (14); A. speciosus (2) | – | [46] |
| Naruko genotype | Wild rats Rodents | None reported | Wild rats (1) | – | [79] |

Note: “–” indicates unknown information; “*” indicates Cryptosporidium spp. that caused the outbreak of human cryptosporidiosis.

3.1.5. C. ubiquitum

C. ubiquitum is considered an emerging zoonotic pathogen. The species has a broad host range that includes primates, carnivores, rodents, and laboratory mice [40,42,43,46,53,62,67,74,77,81]. In the USA, this genotype is considered an emerging human pathogen. In C. ertici, the skunk and muskrat genotypes I and II have also been reported in a few human cases of cryptosporidiosis.

3.2. Zoonotic Cryptosporidium spp. in rodents

A number of other zoonotic Cryptosporidium spp. have been identified in rodents, and several have been identified in humans. Of these, C. muris and C. andersoni are gastric parasites. C. muris has a wide host range that includes various mammals (rodents, canids, felids, suids, equids, NHPs, and marsupials) and birds, but C. andersoni primarily infects cattle, while the human infectivity is controversial. C. tyzzeri mostly infects domestic mice and small rodents, and it has been found in several non-specific hosts such as humans, penguins, black leopards, voles, snakes, and horses, among others [94]. Subtyping of C. tyzzeri at the gp60 locus identified three subtype families (IIa–IV). The chipmunk genotype I has been identified in many rodents and in water [32,40,44,47,48,76]; this genotype is considered an emerging human pathogen. In C. ertici, the skunk and muskrat genotypes I and II have also been reported in a few human cases of cryptosporidiosis.

3.3. Other Cryptosporidium species identified in rodents

Most rodent species and genotypes are host-specific or have narrow host ranges. Specific associations include C. mycotori in nuts [42]; C. pectoralis in moles [46]; C. alticola, C. microti, and vole genotypes I–VII in voles [29,35,37,54]; C. apodemi in mice [37,64]; C. homali and C. weirii in guinea pigs [40,45,47,82]; C. rubiei and squirrel genotypes I–III in ground squirrels [55,77]; C. ratti and mouse genotype II in rats [29,43–45]; hamster genotype in pet hamsters [40,47]; bamboo rat genotypes I–III in bamboo rats [49,50], and apodemus genotypes I and II in Apodemus spp. [37,48]. However, with increasing research effort, the host species ranges of these genotypes (rat genotypes II–V, ferret genotype, chipmunk genotypes II–V, muskrat genotypes I and II, and deer mouse genotypes I–IV) have gradually been extended [13,32,40,44,45,47,52,54,61,65,70,73,77].

C. varani and C. scrofarum have been most often isolated from reptiles and pigs; the presence in rodents may have been the result of mechanical transmission [53,61,87]. Cryptosporidium environmental has been found in wild Apodemus spp., suggesting that the environment plays an important role in transmission dynamics of the parasites [87]. Future studies aiming to characterize Cryptosporidium in environmental samples from areas with rodents are needed. The potential of these Cryptosporidium species and genotypes to cause disease in humans or animals is unknown, but C. ratti, rat genotype III, rat genotype IV, apodemus genotype II, and Cryptosporidium sp. I have been detected in streams in the USA and in raw sewage water in the UK, China, Japan, and USA [13,29,37,94]. To date, these species and genotypes have not been reported in humans, suggesting that they are unlikely to be of public health significance. However, more research is needed to confirm this.
Table 3  
The prevalence of Cryptosporidium and Cryptosporidium spp. in the rodents.

| Animal species                        | Locations total samples no. | Positive/total samples (%) | Cryptosporidium species/genotypes positive no. | gp60 subtypes |
|---------------------------------------|-------------------------------|----------------------------|----------------------------------------------|---------------|
| Brown Rat (Rattus norvegicus)         | Japan (206); England (511); China (491); Iran (106); Nigeria (134); Czech Republic (--) | 17.2% (249/1448) | C. parvum (164); C. ubiquitum (1); C. ratti (37); rat genotype IV (35); C. occultus (5); C. tyzzeri (1); rat genotype III (1); rat genotype V (5); C. muris (4); C. andersoni (4); rat genotype II (1); C. meleagris (1); C. ryanae (1); | IIdA15G1      |
| House Rat (Rattus rattus)             | Japan (346); New Zealand (8); Spain (102); Iran (40); Australia (85) | 26.3% (153/581) | C. parvum (1); rat genotype II/III (10); C. muris (14); C. meleagris (1); C. ratti (1); C. sp. 1 (1) | –             |
| House mouse (Mus musculus)            | England (715); New Zealand (17); USA (303); Spain (78); Iran (63); China (31); Czech Republic (45) | 22.0% (276/1252) | C. muris (61); C. parvum (60); C. tyzzeri (51); C. sp. 2 (1); rat genotype II (2); rat genotype III (2) | Ixa; Ixb      |
| Yellow-necked mouse                   | Poland (331); Spain (2); Belgium (2); Czech Republic (274); Finland (2); France (16); Germany (10); Serbia (14); Slovakia (35); Slovak Republic (196) | 26.2% (66/252) | C. parvum (70); C. ditrichi (43); C. apodemi (11); apodemus genotype I (8); C. tyzzeri (1); apodemus genotype II (4); C. microti (2); C. muris (3); C. scrofarum (5); C. environment (3); C. asiaticum (4) | IlaA8; XVIIa; XVIIa; IlaA16G1Rb; IlaA16G3R1; IlaA10G1R1 |
| Yellow-necked mouse                   | Poland (836); Finland (141); Spain (49); England (123); USA (301) | 30.7% (445/1450) | C. parvum (442); C. muris (2) | –             |
| Common Vole                           | Poland (274); Czech Republic (328); Slovak Republic (75) | 42.8% (290/677) | – | –             |
| Common field vole                     | Finland (131) | 0.8% (1/131) | – | –             |
| Wood mouse (Apodemus sylvaticus)      | England (230); Spain (278); Czech Republic (25); France (4); Netherlands (6); Serbia (3); Slovakia (8) | 30.0% (166/554) | C. parvum (132); C. muris (18); C. ditrichi (3); C. tyzzeri (1); C. apodemi (2) | –             |
| Algerian mouse (Mus agrutus)          | Spain (22) | 27.3% (6/22) | C. parvum (1); C. muris (5) | –             |
| Apodemus speciosus                    | Japan (33) | 12.1% (4/33) | C. muris (2); C. muris novel genotype (2) | –             |
| White-footed mice                     | USA (2706) | 8.2% (222/2706) | C. parvum (165) | –             |
| Red-backed vole                       | USA (5) | 80.0% (4/5) | – | –             |
| Prairie vole (Microtus pennsylvanicus)| USA (307) | 5.2% (16/307) | C. parvum (13) | –             |
| Striped field mouse                   | Slovak Republic (107) | 31.8% (34/107) | C. scrofarum (19); C. environment (2); muscrat genotype II (3); C. parvum (8); C. hominis (1) | –             |
| Muskrat (Ondatra zibethicus)          | Poland (99); USA (353); Spain (90) | 26.3% (119/452) | C. parvum (85); C. muris (5); muskrat genotype I (24); muskrat genotype II (6) | –             |
| California Ground Squirrels           | USA (1162) | 12.8% (149/1162) | C. parvum (149) | –             |
| Eastern Gray Squirrel                 | USA (106) | 17.0% (18/106) | C. parvum (6) | –             |
| Red squirrels (Tamiasciurus hudsonicus)| USA (80); China (333) | 9.4% (39/413) | C. parvum (9); rat genotype II (8); ferret genotype (13); chipmunk genotype III (5); C. ratti (4); | –             |
| Eurasian Red Squirrel                 | Italia (70); USA (2) | 25.0% (18/72) | – | –             |
| Eastern chipmunk                      | USA (268); China (20) | 23.0% (66/288) | ferret genotype (15); chipmunk genotype I (2) | –             |
| Woodchuck (Marmota monax)             | USA (38); Czech Republic (--) | 7.9% (3/38) | C. parvum (2); C. andersoni (1) | –             |
| American Beaver (Castor canadensis)   | USA (170) | 4.1% (7/170) | C. parvum (2) | –             |
| Eurasian Beaver (Castor fiber)        | Poland (82); Slovak Republic (19) | 19.8% (20/101) | C. parvum (16) | –             |
| North American Porcupine (Erethizon dorsatum) | USA (18) | 11.1% (2/18) | C. parvum (2) | –             |
| Cavybara (Hydrochoerus hydrochaeris)  | Brazil (145) | 5.5% (8/145) | C. parvum (8) | –             |
| Root rat (Haplochirocheta splendidii) | Kenya (--) | – | C. proliferans | –             |
| Striped field mouse                   | (A. agrarius) | 16.8% (21/125) | apodemus genotype II (5); C. ditrichi (2); C. apodemi (12); C. parvum (1); C. hominis (1) | XVIIa; IlaA16G1Rb; IlaA10G2 |

(continued on next page)
4. Ecological significance from a One Health perspective

Rodents are essential components of many terrestrial ecosystems. Their beneficial activities in nature are well known, as is their transmission potential of pathogens to humans [92,98–101]. Rodent transfer of pathogens to humans occurs by direct contact with humans and animals or through contamination of human or animal food and water by rodent stools, hair, and urine [9,98,99]. Rodents live in close

| Animal species | Locations | total samples | Positive/total samples (%) | Cryptosporidium species/genotypes positive no. | gp60 subtypes |
|----------------|-----------|---------------|-----------------------------|---------------------------------------------|--------------|
| Guinea pig (Cavia porcellus) | Latvia (11); Lithuania (3); Romania (2); Serbia (4); Slovakia (33); Slovak Republic (72) | China (250); Australia (29); Italia (60); Brazil (5); England (1) | 50.8% (226/445) | C. parvum (1); C. homali (39); C. muris (1); C. parvum (1) | – |
| Chinchilla (Chinchilla lanigera) | China (420); Japan (63) | 11.0% (53/483) | C. ubiquitum (49); C. parvum (3); chimpunk genotype V (1); C. varani (–) | – |
| Djungarian Hamster (Phodopus sungorus) | China (226) | 38.9% (88/226) | hamster genotype (31); C. andersoni (40); C. muris (8); C. parvum (4); C. andersoni + C. parvum (2); C. muris + C. parvum (2) | – |
| Chipmunk (Tamias) | China (4) | 75.0% (3/4) | ferret genotype (2); chimpunk genotype V (1) | – |
| Pteromys volans (Siberian flying squirrel) | China (1) | 100.0% (1/1) | C. ubiquitum (1) | XII |
| Cricetid rodents | USA (586); Czech Republic (493) | 33.2% (362/1089) | – | – |
| Nutria (Myocastor coypus) | Czech Republic (120); Slovak Republic (30) | China (287); USA (302) | 8.0% (12/150) | C. parvum (1); C. ubiquitum (5); C. myocastoris (5) | Ila; XXIb; XXIIa; Xilid; |
| Red-bellied treesquirrels (Gallosciurus erythraeus) | USA (250) | 23.1% (136/589) | C. parvum (1); C. wratj (1); rat genotype II (2); C. rubyi (2); squirel genotypes I (2); squirel genotypes II (1); squirel genotypes III (2); C. ubiquitum (19); skunk genotype (4); deer mouse genotype III (5) | – |
| Bamboo rat (Rhizomys sinensis) | China (1960) | 15.8% (309/1960) | C. parvum (158); C. occultus (8); C. ubiquitum (85); bamboo rat genotype I (54); bamboo rat genotype II (1); bamboo rat genotype III (5); C. muris (1) | IlpA9; IlpA6; IlA15G1; IlA13G1 |
| Porcupine (Hystrix hodgsoni) | China (147) | 6.8% (10/147) | C. tyszery (3); rat genotype III (1) | – |
| Asian house rat (Rattus norvegicus) | China (79) | 50.6% (40/79) | rat genotype IV (24); rat genotype III (8); C. occultus (1); C. erinacei (1); C. parvum (3); C. muris (3) | – |
| Edward’s long-tailed rat (Leopoldamys edwardsi) | China (38) | 55.3% (21/38) | C. viatorum (11); rat genotype IV (8); rat genotype III (2) | XVCa2G1a (4); XVCa2G1b (1); XVdA3 (1) |
| Muridae | China (10) | 40.0% (4/10) | rat genotype III (2); rat genotype IV (2) | – |
| Brandt vole (Microtus brandti) | China (678) | 18.7% (127/678) | C. suis, C. environmental; muskrat genotype II; novel genotype of Brandt’s vole | – |
| Spermophilus ground squirrel | USA (–) | – | C. rubyi (–) | – |
| White-footed Mouse (Peromyscus maniculatus) | USA (1071) | 6.9% (74/1071) | – | – |
| Yellow-bellied Marmot (Marmota flaviventris) | USA (224) | 14.7% (33/224) | C. parvum (33) | – |
| Australian Mice (Mus domesticus) | Australia (250) | 7.6% (19/250) | C. tyszery (6); mouse genotype II (11) | – |
| Indian mole rat (Bambotota bengalensis) | Iran (25) | 36.0% (9/25) | C. muris (9) | – |
| Asian chipmunk (Eutamias sibiricus) | Czech Republic (–) | – | C. muris (–) | – |
| Qinghai vole (Lasioschismys fuscus) | China (90) | 8.9% (8/90) | C. parvum (3); C. canis (1); C. ubiquitum (1); Qinghai vole genotype (3) | – |
| Swamp rats | Australia (21) | 14.3% (3/21) | C. viatorum (3) | XVbA2G1 |
| Prairie vole (Meadow vole) | USA (10) | 10.0% (1/10) | Vole genotype I (1) | – |
| Deer mouse | USA (177) | 32.2% (57/177) | Deer mouse I (13); Deer mouse II (3); Deer mouse III (20); Deer mouse IV (21) | – |
| Laboratory rats | China (355); Czech Republic (–) | 0.6% (2/355) | C. ubiquitum (1); Cryptosporidium spp. (1); C. muris (–) | – |
| Wild rats | Philippines (194); Japan (14); China (228); Poland (266); Malaysia (223); Korea (188) | 33.0% (387/1173) | C. muris (25); C. scrofaform (4); C. ratti (1); rat genotypes II (19); rat genotypes III (23); rat genotypes IV (6); C. occultus (5); C. ubiquitum (10); Naruko genotype (1); C. viatorum (25); C. parvum (13); C. meleagridis (1); chimpunk genotype I (8); bear genotype (14). | XVCaA5; XVCaA3; XVCaA3h; XVCa2G1; IlA15G2R1; IlA17G2R1; IlA16G3R1 |

Note: “–” indicates unknown information.
contact with human populations; farm animals, pets, and peri-urban rodents provide a nexus between wildlife communities and humans, exposing humans to some zoonoses circulating in these natural ecosystems \[99\]. Rodent-borne diseases are associated with the rodent population and human socioeconomic lifestyle factors \[11\]. Human migration, travel, trade, urbanization, and agricultural activities can be facilitating factors in transferring rodent-borne pathogens from one community to another.

4.1. Possible direct transmission of rodent-borne Cryptosporidium at the human–animal–environment interface

Data obtained thus far suggest that rodents may play a role in the transmission of zoonotic Cryptosporidium spp. The first pathway is the direct route in which humans come in contact with Cryptosporidium present in rodent excrement or in an environmental component (food, water, or soil) that is contaminated with rodent urine. Moreover, humans may consume food products or water that is contaminated with rodent feces. Wild rodents are commonly found in urban and rural areas, thus providing a link between rural and urban disease foci \[99\]. Rodent-borne diseases are associated with the rodent population \[99\]. Rodent-borne Cryptosporidium is one of the most prevalent waterborne parasitic infections. Cryptosporidium spores can be transported into water bodies by contact with rodent feces. The figure was originally designed by the authors using ArcGIS 10.2 software. The original vector diagram imported in ArcGIS was adapted from Natural Earth (http://www.naturalearthdata.com).

C. dirichi oocysts were detected in the feces of decoration workers in Sweden. Epidemiological data indicated that the workers shared the same room with wild mice when they were working and thus had contact with mouse feces \[37\]. Humans can be directly infected with Cryptosporidium through contact with rodent feces. Humans often live closely with pet rodents; feeding, handling of rodents, close contact with feces, or playing with rodents can directly cause humans to be infected with Cryptosporidium \(\text{Fig. 2}\). At the same time, pet rodents excrete feces during family activities and thus contaminate the home environment (food, water, and the ground). Humans can become infected with Cryptosporidium by contact with an environment that is contaminated with rodent excrement. Laboratory and farm rodents have close contact with the breeder, and thus the breeder may be directly infected with Cryptosporidium by contacting rodent feces.

4.2. Possible waterborne transmission of rodent-borne Cryptosporidium at the human–animal–environment interface

Cryptosporidium is one of the most prevalent waterborne parasitic infections. Cryptosporidium spores are transported into water bodies by contact with rodent feces. The figure was originally designed by the authors using ArcGIS 10.2 software. The original vector diagram imported in ArcGIS was adapted from Natural Earth (http://www.naturalearthdata.com).

Foodborne illnesses are any infections or diseases caused by consuming contaminated foods or drinks. Almost all reported Cryptosporidium cases of foodborne diseases are caused by C. parvum \[5,97\]. Cryptosporidium foodborne illnesses commonly involve contaminated water supplies, fresh fruits, and vegetables \[10,11,92\]. Polluted waters may contaminate food through the process of irrigating crops and washing vegetables, thereby causing foodborne transmission \[3\] \(\text{Fig. 2}\). Rats within fields excrete feces ubiquitously, thereby increasing the risk for human foodborne illness, particularly if harvested products are to be consumed raw \[3\]. It is difficult to remove Cryptosporidium oocysts from the surfaces of vegetables and fruits using common cleaning methods. Humans may ingest Cryptosporidium under unknown...
circumstances. Unfortunately, there is little relevant research in this area, and thus more research is needed to better understand the potential health risks.

4.4. Possible indirect transmission of rodent-borne Cryptosporidium at the human–animal–environment interface

Rodent-borne pathogens can also be spread indirectly to humans. At least 25 species and 43 genotypes of Cryptosporidium have been detected in rodents; some are zoonotic and can cross the species barrier. In addition to humans, rodent-related zoonotic species and genotypes of Cryptosporidium are present among wildlife, livestock, farm captive animals, and companion animals (Fig. 2). Moreover, rodents can maintain pathogen transmission cycles in different environments. Rodents can serve as potential mediators of Cryptosporidium and can transmit the parasites to wildlife, livestock, farm captive animals, and companion animals.

The risk of Cryptosporidium spreading within a rodent colony is elevated in rodent farms (Cavia porcellus, R. sinensis, and Rattus tanezumi) and laboratory rats that achieve high rodent densities whereby collective fecal production by a cohort, social behaviors (grooming and licking), and close interactions can promote intraspecific transmission, fecal shedding, and environmental persistence of Cryptosporidium. Coprophagia, a common behavior in a variety of rodent species, is a significant route for autoinfection of fecal-orally transmitted Cryptosporidium and can amplify Cryptosporidium shedding and disease spread.
within a rodent colony [92,99]. Wild rats leave many small droppings wherever they forage (including watersheds) in wild areas. Wildlife and domestic animals can become infected with Cryptosporidium by ingesting contaminated food, water, and rodents (possible in carnivores) and thereby transfer the pathogens. At the same time, pet rodents excrete feces during family activities, possibly causing dogs or cats to be infected with Cryptosporidium. Ultimately, humans may be indirectly infected with Cryptosporidium through contact with wildlife, livestock, and companion animals or contaminated environments.

Wild rodents may spread Cryptosporidium on farms. This risk may be even greater on captive animal farms where wild rats can share the habitat with farm animals or travel through grazing land used by domestic animals where contact with livestock is more likely, thus providing ample opportunity for transmission of Cryptosporidium to the livestock. Infected wild rodents on livestock farms can potentially transmit pathogens to the livestock by contaminating animal feed and water sources with fecal pellets. Horizontal transmission by infected captive animals on farms can amplify Cryptosporidium shedding and disease spread. Additionally, rodenticides are used less often on farms, and livestock animals can be involved in the transmission cycle. Studies are required to investigate Cryptosporidium among the diverse human population, livestock, pet animals, and rodents in various ecosystems. Researchers should pursue a multidisciplinary One Health approach with contributions from zoologists, ecologists, veterinarians, and public health experts to understand rodent-related Cryptosporidium and possible transmission routes.

5. Conclusions

Cryptosporidium spp. are common in rodents. To date, 25 Cryptosporidium species and 43 genotypes have been identified in rodents, including the species that cause outbreaks of human cryptosporidiosis, C. parvum and C. hominis. C. parvum is the dominant species in rodents. The fact that zoonotic C. parvum, C. hominis, C. meleagridis, and C. ubiquitum, particularly subtypes IbA10G2 and IIdA15G1, have been found in rodents suggests that rodents infected with Cryptosporidium have significant zoonotic potential. For Cryptosporidium at the human–animal–environment interface, rodents can be a direct route or can become potential mediators in parasite transmission. There is no direct evidence with which to illustrate the transmission pathways of Cryptosporidium at the human–animal–environment interface. In addition to rodents, dogs, cats, wild animals, and livestock animals can be involved in the transmission cycle. Studies are required to investigate Cryptosporidium among the diverse human population, livestock, pet animals, and rodents in various ecosystems. Researchers should pursue a multidisciplinary One Health approach with contributions from zoologists, ecologists, veterinarians, and public health experts to understand rodent-related Cryptosporidium and possible transmission routes.

Search strategy

We conducted a systematic literature search from June 20, 2021 to June 26, 2021 through four databases: PubMed, Scopus, Science Direct, and Web of Science. The search included original field epidemiological articles in English for each of the 86 rodent-Cryptosporidium diseases individually, with no time limit of publication (Supplementary Table S1). The search terms included Cryptosporidium or Cryptosporidiosis and scientific names of animal species We screened the searches as “Title/Abstract” in PubMed, “Find articles with these terms” in Science Direct, “TITLE-ABS-KEY” in Scopus, and “Topic” in Web of Science.

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Declaration of Competing Interest

The authors declare that no competing interests exist.

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