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Zoonotic parasites in farmed exotic animals in China: Implications to public health

Yaqiong Guo [a], Na Li [a], Yaoyu Feng [a,b,**], Lihua Xiao [a,b,*]

[a] Center for Emerging and Zoonotic Diseases, College of Veterinary Medicine, South China Agricultural University, Guangzhou, 510642, China
[b] Guangdong Laboratory for Lingnan Modern Agriculture, Guangzhou, 510642, China

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ABSTRACT

Several species of wild mammals are farmed in China as part of the rural development and poverty alleviation, including fur animals, bamboo rats, and macaque monkeys. Concerns have been raised on the potential dispersal of pathogens to humans and other farm animals brought in from native habitats. Numerous studies have been conducted on the genetic identity and public health potential of *Cryptosporidium* spp., *Giardia duodenalis*, and *Enterocytozoon bieneusi* in these newly farmed exotic animals. The data generated have shown a high prevalence of the pathogens in farmed wildlife, probably due to the stress from the short captivity and congregation of large numbers of susceptible animals. Host adaptation at species/genotype and subtype levels has reduced the potential for cross-species and zoonotic transmission of pathogens, but the farm environment appears to favor the transmission of some species, genotypes, and subtypes, with reduced pathogen diversity compared with their wild relatives. Most genotypes and subtypes of the pathogens detected appear to be brought in from their native habitats. A few of the subtypes have emerged as human pathogens. One Health measures should be developed to slow the dispersal of indigenous pathogens among farmed exotic animals and prevent their spillover to other farm animals and humans.

1. Introduction

Enteric parasites such as *Cryptosporidium* spp., *Giardia duodenalis*, and *Enterocytozoon bieneusi* are important causes of diarrhea (DuPont, 2016). They exsert the highest tolls in young children and neonatal animals (Cho and Yoon, 2014; Collaborators, 2017). As these parasites have a broad host range, they are considered major zoonotic pathogens (Thompson and Smith, 2011). Therefore, the One Health approach has been suggested as a tool in the prevention and control of diseases caused by these pathogens (Krecek et al., 2020; Thompson, 2013). This becomes especially important in the era of COVID-19, when increased attention has been directed to emerging zoonotic pathogens.

Molecular diagnostic tools have used extensively in studies of the transmission of these pathogens (Li et al., 2020c; Xiao and Feng, 2017). Results from characterizations of isolates from humans and various isolates have identified species/genotypes and subtypes with broad host ranges as well as those with host adaptation (Caccio et al., 2018; Feng et al., 2018; Li and Xiao, 2019). As a result, the cross-species transmission and public health potentials of various *Cryptosporidium* species, *G. duodenalis* genotypes (known as assemblages), and *E. bieneusi* genotypes are different. For example, among the over 40 known *Cryptosporidium* species and an equal number of genotypes of unknown species status, only *C. parvum*, *C. hominis*, *C. meleagridis*, *C. canis*, and *C. felis* are major human pathogens (Zahedi and Ryan, 2020). Similarly, among the at least seven assemblages (A to H) of *G. duodenalis* from mammals, only assemblages A and B are major human pathogens (Caccio et al., 2018). Furthermore, only Group 1 genotypes among the nearly 500 *E. bieneusi* genotypes in 11 genogroups are major human pathogens (Li et al., 2019b). Therefore, not all species, genotypes, and subtypes of these pathogens have zoonotic potentials.

Wildlife has been suggested to play important roles in the ecology and transmission of *Cryptosporidium* spp., *G. duodenalis*, and *E. bieneusi* (Appelbee et al., 2005; Li and Xiao, 2021). The similar distribution of *Cryptosporidium* species and *G. duodenalis* and *E. bieneusi* genotypes between humans and wild mammals indicates that there could be frequent cross-species transmission of these pathogens (Lesnianska and

* Corresponding author. Center for Emerging and Zoonotic Diseases, College of Veterinary Medicine, South China Agricultural University, Guangzhou, 510642, China.
** Corresponding author. Guangdong Laboratory for Lingnan Modern Agriculture, Guangzhou, 510642, China.
E-mail addresses: yyfeng@scau.edu.cn (Y. Feng), lxiao@scau.edu.cn (L. Xiao).

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Perec-Matysiak, 2017; Thompson and Ash, 2016). Some of the wildlife of major concern are rodents, nonhuman primates, and carnivores, as they are in closer contact with humans than other animals. As a result, numerous studies have been conducted on the molecular characterization of *Cryptosporidium* spp., *G. duodenalis*, and *E. bieneusi* in these animals (Innes et al., 2020; Lesnianska and Perec-Matysiak, 2017). Many such studies were from China because of the increased awareness of wildlife as potential reservoirs of zoonotic parasites (Chen et al., 2019a, 2019b; Huang et al., 2019; Karim et al., 2014c, 2015b; Li et al., 2016a; Lv et al., 2009; Song et al., 2018; Ye et al., 2012; Zhao et al., 2015b, 2020).

Terrestrial wild mammals are bred and farmed in China as part of the national policy for rural development and poverty alleviation. The value of commercial breeding and farming of terrestrial wildlife in China was estimated to be $11.4 billion in 2018 (You, 2020). In northern China, several species of fur animals such as blue and silver foxes, raccoon dogs, and minks are farmed in China (Zhao et al., 2015a). Similarly, some nonhuman primates such as crab-eating and rhesus macaques are farmed as laboratory animals and bamboo rats for food (Chen et al., 2019a; Li et al., 2020a). As they are recently domesticated wild mammals, concerns have been raised about their potential to transmit human pathogenic parasites (Wang et al., 2019; Yang et al., 2015, 2017; Zhang et al., 2018). In the present report, we have summarized data from recent molecular epidemiological studies of *Cryptosporidium* spp., *G. duodenalis*, and *E. bieneusi* for improved understanding of the public health significance of the pathogens in these farmed exotic animals.

2. *Cryptosporidium* spp. in farmed exotic animals

Cryptosporidium spp. have been commonly identified in farmed fur animals, bamboo rats, and macaque monkeys in China (Table 1). The reported infection rates varied greatly among studies for each species of the animals examined (Table 1). This has been attributed to levels of hygiene in the study facilities (Li et al., 2020b). The highest infection rates were reported as 9.1% in crab-eating macaques, 15.9% in foxes, 20.5% in raccoon dogs, 29.4% in bamboo rats, and 29.6% in minks (Table 1). They are much higher than infections rates of *Cryptosporidium* spp. obtained from wild populations of these animals in China and other countries, possibly due to the short history of domestication and congregations of many susceptible animals in confirmed spaces. As expected, young animals were reported to have higher prevalence of *Cryptosporidium* spp. than older animals (Chen et al., 2019a; Li et al., 2020a, 2020b; Qian et al., 2020; Zhang et al., 2016a; Zhao et al., 2019). In crab-eating macaques, animals with diarrhea had higher occurrence of *Cryptosporidium* infection (Chen et al., 2019a).

2.1. *Cryptosporidium* species and subtypes in fur animals

Several *Cryptosporidium* species and genotypes were detected in farmed foxes, raccoon dogs, and minks in China. One dominant species in these fur animals is *C. canis*, which was found in most studies conducted in northern China. In addition, *Cryptosporidium* mink genotype appears to be another common pathogen in minks. Other

Table 1
Distribution of *Cryptosporidium* species/genotype in farmed exotic animals in various studies in China.

Host	Location	No. of specimens	No. positive for *Cryptosporidium* (%)	Species/genotype (no.)	Reference
Mink	Xinjiang	214	26 (12.1%)	Mink genotype (17), *C. canis* (7); *C. parvum* (2)	Qian et al. (2020)
	Heilongjiang, Jilin, Liaoning	114	8 (7.0%)	*C. canis* (6), mink genotype (2)	Yang et al. (2018)
	Heilongjiang	162	48 (29.6%)	*C. canis* (19), mink genotype (18) *C. meleagridis* (3)	Zhang et al. (2016a)
	Hebei	469	6 (1.3%)	Mink genotype (6)	Wang et al. (2008)
Raccoon dog	Xinjiang	39	8 (20.5%)	*C. canis* (8)	Qian et al. (2020)
	Heilongjiang, Jilin	40	0	–	Yang et al. (2018)
	Heilongjiang	162	17 (10.5%)	*C. canis* (15)	Zhang et al. (2016a)
Fox	Xinjiang	35	1 (2.9%)	*C. canis* (1)	Qian et al. (2020)
	Heilongjiang, Jilin, Liaoning	213	12 (5.6%)	*C. canis* (11) *C. meleagridis* (1)	Yang et al. (2018)
	Heilongjiang	191	3 (1.6%)	*C. canis* (3)	Zhang et al. (2016a)
	Hebei, Jilin, Heilong	302	48 (15.9%)	*C. canis* (48)	Zhang et al. (2016c)
Crab-eating macaque	Hainan	1452	132 (9.1%)	*C. hominis* (86), *C. parvum* (30), *C. muris* (15), *C. ubiquitum* (1)	Chen et al. (2019a)
	Hainan	193	11 (5.7%)	*C. hominis* (11)	Zhao et al. (2019)
	Guangxi	205	1 (0.5%)	*C. hominis* (1)	Ye et al. (2014)
	Guangdong	57	1 (1.8%)	*C. hominis* (1)	Karim et al. (2014c)
Rhesus macaque	Henan, Guangxi	1144	9 (0.8%)	*C. hominis* (9)	Karim et al. (2014c)
	Hainan	30	0	-	Zhao et al. (2019)
Bamboo rat	Sichuan	92	3 (3.3%)	*C. parvum* (3)	Liu et al. (2015)
	Hunan, Jiangxi, Chongqing, Guangxi, Guangdong	435	9 (2.1%)	Bamboo rat genotype I (5), *C. parvum* (2), *C. occultus* (1), bamboo rat genotype II (1)	Wei et al. (2019)
	Jiangxi, Guangxi, Hainan	709	209 (29.4%)	Bamboo rat genotype I (85), *C. parvum* (78), bamboo rat genotype III (45), *C. occultus* (1)	Li et al. (2020a)
	Guangdong	724	88 (12.2%)	Bamboo rat genotype I (49), *C. parvum* (31), bamboo rat genotype III (5), *C. occultus* (2), *C. muris* (1)	Li et al. (2020b)

Cryptosporidium species identified include *C. parvum* and *C. meleagridis* in a few animals (Table 1). The *C. parvum* identified in two minks belonged to IIdA15G1, one of the two most common *C. parvum* subtypes in China (Qian et al., 2020). Four divergent subtype families (Xb-Xe) were found in *Cryptosporidium* mink genotype, indicting the diverse origins of these animals (Qian et al., 2020; Yang et al., 2018; Zhang et al., 2016a).

2.2. *Cryptosporidium species and subtypes in bamboo rats*

Similarly, several *Cryptosporidium* species and genotypes were found in farmed bamboo rats in China. Among them, *C. parvum* was one of the dominant species in the a few studies conducted in southern China. Other common genotypes include *Cryptosporidium* bamboo rat genotypes I and IIII, which are genetically related to *C. ubiquitum* and *C. parvum*, respectively (Li et al., 2020b). The remaining species and genotypes (*C. occultus*, *C. muris*, and bamboo rat genotype II) have been found in only a few animals (Table 1), thus could represent native parasites of other rodents. In the latter, bamboo rat genotype is genetically similar to a genotype in found in a masked palm civet (Yu et al., 2020). The intensity of oocyst shedding was higher when animals were infected with *C. parvum* and *C. parvum*-like genotype (bamboo rat genotype III) than with other *Cryptosporidium* spp. (Li et al., 2020a, 2020b).

The *C. parvum* subtypes found in bamboo rats belong mostly to two divergent subtype families (IIo and IIp) of *C. parvum*, which are genetically related to the IId subtype family and have been thus far reported only in Asia (Li et al., 2020a; Liu et al., 2015; Wei et al., 2019). Two subtypes of each subtype family have been identified in bamboo rats from various areas, including IIoA13G1, IIoA15G1, IIpA6 and IIpA9 (Li et al., 2020a, 2020b; Liu et al., 2015; Wei et al., 2019). One bamboo rat was identified as having the *C. parvum* IIdA15G1 subtype (Wei et al., 2019).

2.3. *Cryptosporidium species and subtypes in macaques*

Four *Cryptosporidium* species have been identified in farmed macaques, mostly in southern China. They include *C. hominis*, *C. parvum*, *C. muris* and *C. ubiquitum*. The dominant species is *C. hominis*, which was identified in all studies conducted in farmed crab-eating and rhesus macaques (Table 1). Other *Cryptosporidium* species were only detected in one study conducted in crab-eating macaques on a large farm in Hainan (Chen et al., 2019a). On that farm, significant number of animals were infected with *C. parvum* and *C. muris* in addition to *C. hominis*. The intensity of oocyst shedding was higher in animals infected with *C. hominis* than those infected with *C. parvum* and *C. muris* (Chen et al., 2019a).

The *C. hominis* subtypes detected in farmed macaques all belong to the unique *C. hominis* monkey genotype with divergent small subunit (SSU) rRNA gene sequence (Chen et al., 2019a; Feng et al., 2018; Karim et al., 2014c; Zhao et al., 2019). At the *gp60* locus, they were from three unusual subtype families of Ii (IiA17), Im (ImA18), and In (InA14, InA17, and InA26), and one common subtype family Ib (Chen et al., 2019a; Karim et al., 2014c; Zhao et al., 2019). The Ib subtype identified at the *gp60* locus was IbA12G3, which at the SSU rRNA locus was identified as *C. hominis* monkey genotype (Karim et al., 2014c). Other subtypes of the Ib subtype family in humans have the typical SSU rRNA sequences of *C. hominis* (Feng et al., 2018). The *C. parvum* identified in crab-eating macaques belong to IIoA14G1 (n = 18) and IIdA19G1 (n = 2). Of clinical significance, *C. hominis* ImA18 subtype and *C. parvum* IIoA14G1 subtype were detected in animals with diarrhea whereas the remaining ones were mostly found in asymptomatic animals (Chen et al., 2019a).

3. *Giardia duodenalis* in farmed exotic animals

Several studies were conducted to assess the prevalence and genotype identity of *G. duodenalis* in farmed raccoon dogs, bamboo rats, and macaque monkeys in China. Low infections rates were obtained from most studies (Table 2). Two studies, however, showed common occurrence of *G. duodenalis* in farmed crab-eating macaques (32.3%) in Hainan and bamboo rats (10.8%) in Hunan. Younger animals and animals with diarrhea had higher infection rates than older animals and animals with normal stools (Chen et al., 2019b; Ma et al., 2018). Infected raccoon dogs mostly had assemblage C, while macaque monkeys and bamboo rats mostly had assemblage B (Table 2). There was a high genetic diversity among assemblage B and C isolates in all these studies (Chen et al., 2019b; Karim et al., 2014c; Ma et al., 2018; Ye et al., 2014; Zhang et al., 2016d). In one study of *G. duodenalis* in crab-eating macaques on one farm, 53 multi-locus genotypes were found. Most of them were genetically related to those previously seen in Old-World monkeys (Chen et al., 2019b; Karim et al., 2014c).

4. *Enterocytozoon bieneusi* in farmed exotic animals

The transmission of *E. bieneusi* in farmed exotic animals in China has been examined in numerous studies. *E. bieneusi* was commonly detected in farmed fur animals in northern China and bamboo rats and macaque monkeys in southern China (Table 3). The reported infection rates were mostly above 10%. This was especially the case with macaque monkeys (Table 3). Unlike the case with *Cryptosporidium* spp. and *G. duodenalis*, there were no consistent age-associated differences in infection rates of *E. bieneusi*, which was detected at high frequency in all age groups of animals sampled in most studies (Chen et al., 2019b; Ma et al., 2020a, 2020b; Yang et al., 2015; Ye et al., 2014; Zhang et al., 2016b, 2018). Crab-eating macaques with diarrhea were reported to have higher infections rates than those with normal stools (Chen et al., 2019b).

4.1. *E. bieneusi genotypes in farmed fur animals*

A high genetic diversity is present in *E. bieneusi* isolates from farmed minks, foxes, and raccoon dogs. Most of these studies have reported multiple genotypes in each species of animals on each farm (Table 3). Altogether, 25 *E. bieneusi* genotypes have been found in the small numbers of foxes, racoon dogs and minks examined in northern China. They all belong to Group 1, and many occur in multiple animal species. D, however, appears to be the dominant genotype in farmed fur animals, being found in all but one study (Table 3). Although concerns have been raised regarding the public health significance of *E. bieneusi* from fur animals based on the wide occurrence of the well-known zoonotic genotype (Yang et al., 2015), multilocus characterization of *E. bieneusi* of ITS genotypes A, D and Type IV at four micro and minisatellites (MS1, MS3, MS4 and MS7) had shown clear genotypic and phylogenetic divergences between isolates of ITS genotype D from fur animals and humans. In fact, in phylogenetic analysis of the multilocus sequence data, genotype D isolates from fur animals formed their own cluster, while human isolates of genotype D clustered together with Type IV from humans from several countries. A third cluster was formed by isolates of the anthroponotic genotype A. While the first two populations had clonal genetic structure, the third population had an epidemic genetic structure (Li et al., 2016b). The presence of host-segregated *E. bieneusi* genotypes was supported by MLST analysis of additional isolates from other hosts (Li et al., 2019a; Liu et al., 2020). These data indicate significant population differentiation of *E. bieneusi* between fur animals and humans within some of the so-called zoonotic ITS genotypes.

4.2. *E. bieneusi genotypes in bamboo rats*

There were only two studies of *E. bieneusi* in bamboo rats in southern China. Altogether, eight genotypes were found among the small number of positive samples. The dominant genotype was D. Other Group 1 genotypes included the well-known Peru11, EbpA, and PigEBITS7. Two novel genotypes of Group 2, however, were detected in a few animals

Table 2
Distribution of *Giardia duodenalis* assemblages in farmed exotic animals in various studies in China.

Host	Location	No. of specimens	No. positive for *G. duodenalis* (%)	Assemblage (no.)	Reference
Raccoon dog	Heilongjiang, Jilin, Liaoning, Hebei, Shandong	305	22 (7.2%)	C (22)	Zhang et al. (2016d)
Crab-eating macaque	Hainan	1452	469 (32.3%)	B (469)	Chen et al. (2019b)
	Guangxi	205	5 (2.4%)	A (2), B (3)	Ye et al. (2014)
	Guangdong	57	1 (1.8%)	B (1)	Karim et al. (2014c)
Rhesus macaque	Henan, Guangxi	1144	20 (1.7%)	B (20)	Karim et al. (2014c)
Bamboo rat	Hunan	480	52 (10.8%)	B (52)	Ma et al. (2018)

Table 3
Distribution of *Enterocytozoon bieneusi* genotypes in farmed exotic animals in various studies in China.

Host	Location	No. of specimens	No. positive for *E. bieneusi* (%)	Genotype (no.)[a]	Reference
Mink	Heilongjiang, Jilin, Liaoning, Hebei, Shandong	298	30 (10.1%)	**D** (12), **Peru11** (5), **EbpC** (7), **NCM-1** (5), **NCM-2** (1)	Zhang et al. (2018)
Raccoon dog	Shandong	356	23 (6.5%)	**Type IV** (11), **D** (8), **Peru8** (3), **CHG1** (1)	Ma et al. (2020a)
	Heilongjiang, Jilin, Liaoning, Hebei, Shandong	305	68 (22.3%)	**NCF2** (33), **CHN-F1** (10), **D** (9), **CHN-DC1** (9), **NCR2** (5), **NCR1** (2)	Xu et al. (2016)
	Heilongjiang	49	2 (4.1%)	**D** (1), **CHN-R1** (1)	Zhao et al. (2015a)
	Heilongjiang	162	17 (10.5%)	**D** (14), **CHN-DC1** (1), **CHN-DC1/WildBoar3** (1)	Yang et al. (2015)
Fox	Shandong	344	31 (9.0%)	**HND-1** (10), **NCF2** (5), **Type IV** (3), **Hum-q1** (1), **SDF1** (1), **SDF2** (1)	Ma et al. (2020b)
	Heilongjiang, Jilin, Hebei	302	37 (12.3%)	**NCF2** (13), **Peru8** (4), **Type IV** (5), **D** (4), **NCF1** (3), **CHN-DC1** (2), **NCF5** (2), **NCF3** (1), **NCF4** (1), **NCF6** (1), **NCF7** (1)	Zhang et al. (2016b)
	Heilongjiang, Jilin	110	18 (16.4%)	**D** (12), **EbpC** (5), **CHN-F1** (1)	Zhao et al. (2015a)
	Heilongjiang	191	53 (27.7%)	**D** (44)	Yang et al. (2015)
Crab-eating macaque	Hainan	1452	461 (31.7%)	**Type IV** (236), **Macaque3**[b] (119), **Peru8** (42), **Pongo2** (27), **CM2** (17), **Peru11** (12), **D** (4) **CM3** (3), **PigEbITS7** (1)	Chen et al. (2019b)
	Beijing	133	34 (25.6%)	**Type IV** (10), **Macaque3**[b] (9), **CM2** (4), **D** (3), **Peru11** (3), **Peru8** (2), WL21 (1), **CC4** (1), **D/Peru11** (1), **Peru8/Type IV** (1), **CMB1** (1), **CMB2** (1)	Yang et al. (2017)
	Guangxi	205	38 (18.5%)	**D** (16), **Macaque3** (15), **Macaque4** (2), **Peru11** (2), **WL15** (1)	Ye et al. (2014)
	Guangdong	57	40 (70.2%)	**Type IV** (15), **Macaque3**[b] (14), **Peru8** (3), **CM2** (3), **D** (2), **Peru11** (2), **CM3** (1)	Karim et al. (2014a)
Rhesus macaque	Sichuan, Guangxi, Yunan	427	53 (12.4%)	**Macaque3**[b] (25), **Type IV** (15), **D** (9), **Peru8** (4)	Karim et al. (2014a)
White-headed langur	Guangxi	143	19 (13.3%)	**D** (11), **Macaque3**[b] (4), **Peru8** (2), **CM2** (1), **Peru11** (1)	Karim et al. (2014a)
Bamboo rat	Hainan	117	18 (15.4%)	**D** (15), **Peru11** (1), **HNR-IV** (1), **HNR-V** (1)	Zhao et al. (2020)
	Hunan, Jiangxi, Chongqing, Guangxi, Guangdong	435	22 (5.1%)	**D** (17), J (1), BR1 (1), BR2 (1), **EbpA** (1), **PigEBITS7** (1)	Wang et al. (2019)

[a] Bolded ones are Group 1 genotypes.
[b] Reported as CM1.

(Wang et al., 2019), indicating that the ITS genotype D could be from a source different from that in fur animals.

4.3. *E. bieneusi* genotypes in farmed monkeys

E. bieneusi infections are especially common in farmed monkeys. Studies conducted in three species of farmed monkeys have identified 15 *E. bieneusi* genotypes, all belonging to Group 1. Macaque3 (synonym of CM1) was the dominant genotype in most studies (Table 3). Other common genotypes include Type IV, D and Peru8, all well-known zoonotic ITS genotypes. There are no apparent differences in the distribution of *E. bieneusi* genotypes among the three species of farmed monkeys examined. This contrasts with the dominance of Peru11 and absence of Macaque3 in free-range monkeys in a public park in Guiyang, China (Ye et al., 2012). Similarly, in a study of various nonhuman primates in zoos in China, D was the dominant *E. bieneusi* genotype in most animals, while Macaque3 was only seen in macaque monkeys (Karim et al., 2015a). In another study conducted in a zoo in Zhengzhou, Henan, all three species of monkeys were mainly infected with HenanV. Therefore, the distribution of *E. bieneusi* genotypes in farmed monkeys appears to be different from that in captive monkeys kept in zoos and parks.

Multilocus sequence typing (MLST) of 85 of *E. bieneusi* isolates from diverse nonhuman primates produced 59 multilocus genotypes. They formed four subpopulations in phylogenetic and STRUCTURE analyses, all with an epidemic genetic structure. Among them, sub-population 1 contained mainly ITS genotype Type IV, sub-population 2 contained mainly ITS genotypes Macaque3 (CM1) and D, sub-population 3 contained mixed genotypes, while sub-population 4 contained genotype Henan V (Karim et al., 2014b). This was supported by recent population genetic analyses of *E. bieneusi* from nonhuman primates and ruminants in China (Chen et al., 2020; Zhang et al., 2020).

5. Public health perspectives of zoonotic protists in farmed exotic animals

Data accumulated thus far have shown a prevalence of *Cryptosporidium* spp., *G. duodenalis*, and *E. bieneusi* in farmed exotic animals. Molecular characterizations of isolates from these animals have identified the occurrence of human-pathogenic species/genotypes and subtypes. The public health significance of these enteric protists depends on the distribution of genotypes and/or subtypes. This is further impacted by the species of animals under consideration. Therefore, data from individual pathogens and farm animals are needed for accurate assessment of public health potential of pathogens in farmed exotic animals.

While we appreciate the human-infective potential of enteric protists from farmed animals, host specificity in pathogens might have reduced the likelihood for zoonotic infections in humans and cross-species transmission of pathogens among animals. For example, the dominant *C. canis* species in farmed fur animals is unlikely to cause major outbreaks in humans, which thus far are caused almost exclusively by the more virulent and infectious *C. parvum* and *C. hominis*. The canine-adapted nature of *C. canis* suggests that it is also unlikely to be a major pathogen in macaque monkeys and bamboo rats, which are farmed in southern China. The same is likely true for the assemblage C of *G. duodenalis* identified in farmed fur animals, which is not an established pathogen in humans and has rarely been found in monkeys and bamboo rats.

Host adaptation within pathogen species or genotypes could further reduce the occurrence of cross-species transmission. For example, the *C. hominis* variants infecting monkeys are not the subtypes commonly found in humans. The two differ from each other in the SSU rRNA sequences in addition to belonging to different subtype families at the *gp60* locus. Similarly, although monkeys and other nonhuman primates are commonly infected with assemblage B subtypes of *G. duodenalis*, results of the MLST analyses indicate that they differ from those found in humans genetically. Host-adapted subpopulations have further been found in *E. bieneusi* isolates from farmed monkeys. While fur animals, monkeys and bamboo rats appear to be commonly infected with human-pathogenic genotypes of *E. bieneusi*, the presence of host-adapted subpopulations in some of the zoonotic ITS genotypes such as D implies that cross-species transmission might not occur as widely as believed.

Results of genotype analyses suggest that most of the enteric protists in farmed wildlife were probably brought from their native habitats. The *C. hominis* identified in farmed macaque monkeys all belong to several subtype families (Ii, Im, and In) of the monkey genotype, which have not been found in other farm animals. Similarly, the dominant genotype of *E. bieneusi* in nonhuman primates in China, Macaque3, has rarely been found in other animals and never in humans (Chen et al., 2020). As discussed above, the assemblage B of *G. duodenalis* from farmed macaques formed a cluster with sequences from Old World monkeys. A similar situation is seen with pathogens in farmed bamboo rats, which are commonly infected with very divergent *Cryptosporidium* spp. (bamboo genotypes I, II, and III) and occasionally infected with *Cryptosporidium* spp. from other rodents (*C. muris* and *C. occultus*). When they are infected with *C. parvum*, the subtypes involved are mostly IIo and IIp subtypes, which are distinct to the IIa and IId subtype families found in other farm animals. As there are divergent subtype families within *C. canis*, it would be interesting to see whether the *C. canis* isolates in farmed fur animals belong to host-adapted subtype families, as suggested recently on *C. canis* isolates from foxes in the United States (Jiang et al., 2020).

The farm environment appears to promote the transmission of *Cryptosporidium* spp. with high transmissibility. This is reflected by the difference in the distribution of *Cryptosporidium* species and subtypes between farmed and wild animals. For example, farmed raccoon dogs, foxes, and minks are most infected with *C. canis* (Table 1), which in native habitats are only found in dogs, foxes and other canine animals (Zhou et al., 2004). Wild raccoon dogs, foxes, and minks, in contrast, are infected with a range of *Cryptosporidium* species such as *C. parvum*, *C. hominis*, *C. ubiquitum*, *C. andersoni*, *C. felis*, *C. suis*, and muskrat genotype I, which are rarely seen in farmed fur animals (Barrera et al., 2020; Gomez-Couso et al., 2007; Kellnerova et al., 2017; Mateo et al., 2017; Matsubayashi et al., 2005; Nagano et al., 2007; Stuart et al., 2013; Zhou et al., 2004). As minks, raccoon dogs and foxes are frequently kept in proximity, it is possible that foxes might have transmitted *C. canis* to minks and raccoon dogs in captivity. There could be cross-species transmission of *C. parvum* between farmed bamboo rats and macaque monkeys as well. Both are commonly infected with IIo and IIp subtypes of *C. parvum*, which are divergent subtype families rarely found in other animals (Chen et al., 2019a; Li et al., 2020a, 2020b; Liu et al., 2015; Wei et al., 2019). This was supported by the dominance of *G. duodenalis* assemblage B in both group of animals (Table 2). Further studies using advanced molecular typing and comparative genomics are needed to valid these suggestions.

Measures should be developed to prevent the spillover of the enteric protists from the farmed exotic animals to humans and other farm animals. As discussed above, some of the divergent *C. parvum* subtypes, such as IIo and IIp, have already been spread from bamboo rats to macaque monkeys. Between them, two IIo subtypes have been identified in seven human patients in Thailand and New Zealand (Garcia et al., 2020; Insulander et al., 2013; Sannella et al., 2019). Previously, rodents were suggested to play a major role in the dissemination of *C. parvum* IId subtypes to farm animals and humans in China (Feng and Xiao, 2017). Among *C. hominis* detected in farmed macaque monkeys, the IiA17 subtype has been reported in a few human cases (Elwin et al., 2012; Lebbad et al., 2018). Another subtype commonly detected in nonhuman primates, IbA12G3, is emerging as a major subtype for human cryptosporidiosis in the United Kingdom, Ireland, Canada, Mexico, and Australia (Chalmers et al., 2019; Guy et al., 2021; Millan et al., 2019; O' Leary et al., 2020; Urrea-Quezada et al., 2018). This subtype could be a genetic recombinant, as isolates from farmed macaques differed from human isolates at the SSU rRNA locus. Genetic recombination has been implicated in the emergence of hyper-transmissible *C. hominis* subtypes in humans (Guo et al., 2015).

Since the beginning of COVID-19, the Chinese government has tightened regulations on the breeding and farming of exotic animals (You, 2020). Captive wild animals are no longer farmed for meat and consumption of exotic meat becomes illegal. As a result, the farming of bamboo rats has been forbitten in China and the breading of other animals requires special licenses and is subject to more stringent monitoring. Another newly established biosafety law has set specific guidelines on the surveillance of major and emerging diseases in farmed exotic animals. The implementation of these new legislations would probably reduce the emergence of new pathogens in farmed exotic animals. One Health measures, including molecular surveillance systems and better training and education of farmers, should be developed to control the transmission of indigenous pathogens among farmed terrestrial wildlife and spillover of infections to other farm animals and humans.

Declaration of competing interest

The authors declared that they have no conflicts of interest with this work.

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