International Journal for Parasitology: Parasites and Wildlife 5 (2016) 76–87

Contents lists available at ScienceDirect

International Journal for Parasitology: Parasites and Wildlife

journal homepage: www.elsevier.com/locate/ijppaw

Review

More than a rabbit's tale – *Encephalitozoon* spp. in wild mammals and birds

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ARTICLE INFO

Article history:
Received 30 October 2015
Received in revised form
23 December 2015
Accepted 5 January 2016

Keywords:
Encephalitozoon cuniculi
Encephalitzoon hellem
Encephalitozoon intestinalis
Genotype
Zoonosis
Reservoir

ABSTRACT

Within the microsporidian genus *Encephalitozoon*, three species, *Encephalitozoon cuniculi*, *Encephalitozoon hellem* and *Encephalitozoon intestinalis* have been described. Several orders of the Class Aves (Passeriformes, Psittaciformes, Apodiformes, Ciconiiformis, Gruiformes, Columbiformes, Suliformes, Podicipediformes, Anseriformes, Struthioniformes, Falconiformes) and of the Class Mammalia (Rodentia, Lagomorpha, Primates, Artyodactyla, Soricomorpha, Chiroptera, Carnivora) can become infected. Especially *E. cuniculi* has a very broad host range while *E. hellem* is mainly distributed amongst birds. *E. intestinalis* has so far been detected only sporadically in wild animals. Although genotyping allows the identification of strains with a certain host preference, recent studies have demonstrated that they have no strict host specificity. Accordingly, humans can become infected with any of the four strains of *E. cuniculi* as well as with *E. hellem* or *E. intestinalis,* the latter being the most common. Especially, but not exclusively, immunocompromised people are at risk. Environmental contamination with as well as direct transmission of *Encephalitozoon* is therefore highly relevant for public health. Moreover, endangered species might be threatened by the spread of pathogens into their habitats. In captivity, clinically overt and often fatal disease seems to occur frequently. In conclusion, *Encephalitozoon* appears to be common in wild warm-blooded animals and these hosts may present important reservoirs for environmental contamination and maintenance of the pathogens. Similar to domestic animals, asymptomatic infections seem to occur frequently but in captive wild animals severe disease has also been reported. Detailed investigations into the epidemiology and clinical relevance of these microsporidia will permit a full appraisal of their role as pathogens.

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http://dx.doi.org/10.1016/j.ijppaw.2016.01.001

1. Introduction

With their broad host spectrum and often poor host specificity, microsporidia receive increasing scientific attention as pathogens of humans and animals. Recent developments in molecular diagnostics and phylogenetic analyses now allow for the screening of large numbers of samples for microsporidial infections and yield detailed information on different genotypes and their relationships. This gives a clearer picture on host specificity, transmission pathways and zoonotic risks (Deplazes et al., 2000; Ghosh and Weiss, 2009).

Since the first description of clinically overt infection in human patients with AIDS (for a review see Kotler and Orenstein, 1999), microsporidia including *Encephalitozoon* spp. have been recognised as opportunistic pathogens and further research revealed infections also in non-immunocompromised humans (Cotte et al., 1999; Didier and Weiss, 2011).

Within the genus *Encephalitozoon*, three species have been described in mammals and birds (for a review see Didier, 2005; Mathis et al., 2005), *Encephalitozoon cuniculi*, *Encephalitozoon hellem* and *Encephalitozoon intestinalis*. *E. cuniculi* infections of pet rabbits and laboratory rabbits are best described (for review see (Künzel and Joachim, 2010)). However this species can also infect several other mammals (Wasson and Peper, 2000; Levkutová et al., 2004; Mathis et al., 2005; Goodwin et al., 2006; Lindsay et al., 2009; Sasaki et al., 2011; Wagnerová et al., 2012; Cray and Rivas, 2013; Meng et al., 2014).

In contrast to infections of humans and domestic animals, comparatively little is known about the situation in wild animals. As the awareness of the role of wildlife as a source of infectious agents for human and animal health is growing, so is research on this topic (Thompson, 2013). Infections of wild animals are not only considered a possible threat to human and animal health, but also an issue concerning wildlife conservation since infections with pathogens not previously encountered might be detrimental to wild animal species themselves. This is of special concern to endangered species that might become infected through the intrusion of infected hosts into their habitat (Thompson, 2013).

Until now, the sylvatic cycles of *Encephalitozoon* spp. are largely unknown, but understanding the epidemiology of these pathogens is a crucial step for controlling microsporidial infections. In this review, we want to give an overview of the occurrence of *Encephalitozoon* spp. in wildlife and discuss the possibility of cross-species (zoonotic and animal-to-animal) transmission. We focus on wild mammals and wild birds and included both non-domesticated animals living in their natural environment as well as captive animals.

2. Encephalitzoon: species, diagnosis and transmission

2.1. Encephalitozoon species

Spores of *Encephalitozoon* spp. are morphologically indistinguishable from each other. While *E. cuniculi* has already been described in 1923, the detection of further species of the genus *Encephalitozoon* was not made before the early 1990s when molecular analyses allowed identification and discrimination on the species level.

2.1.1. Encephalitozoon cuniculi

E. cuniculi can be assumed to circulate in rabbit populations worldwide and has the broadest host range, mainly among the non-human Mammalia, but also in birds and humans. Four different strains have so far been differentiated by analysis of the ITS region of ribosomal genes, although there seems to be a certain host preference in each strain this specificity is not strict (Selman et al., 2013). Strain I ("rabbit strain") is found predominantly in rabbits; strain II ("mouse strain") is found in rodents but also in blue foxes and cats; strain III ("dog strain") has been shown to cause high mortality in monkeys, steppe lemmings and dogs. The recently discovered strain IV ("human strain") has so far been found in humans, cats and dogs (Talabani et al., 2010; Nell et al., 2014, 2015).

Humans have been found to be infected with all known strains (although only rarely with strain III). It is most likely that infections with *E. cuniculi* are predominantly zoonotic (Shadduck et al., 1979; Didier, 2005; Mathis et al., 2005; Didier and Weiss, 2011; Sokolova et al., 2011).

2.1.2. Encephalitozoon hellem

E. hellem was first described as the cause of keratoconjunctivitis in a human AIDS patient but its broadest distribution can be found amongst birds. Monkeys, carnivore and rodents can also be infected by this species (Tables 1, 2, 4 and 5). Different genotypes can be distinguished using three different gene loci: Mathies distinguished three genotypes (named 1,2,3) using internal transcribed spacer (ITS) sequences (Mathies et al., 1999). Later Xiao et al. (2001) could further distinguish these genotypes by additionally targeting the polar tube protein gene locus and the small subunit rRNA gene: The former genotype 1 could be distinguished in 1A, 1B, 1C; genotype 2 was distinguished into 2A and 2B moreover genotype 3 was suggested to be renamed 2C. There are further intraspecies variations so that more genotype variants can be described (Haro et al., 2003). Distinguishing the genotypes could be helpful to exclude or suggest infections of a common origin (Haro et al., 2006a).

Table 1
Encephalitozoon spp. identified in wild Aves. PCR – polymerase chain reaction; M – Microscopy; IF – immunofluorescence; FISH – fluorescent in situ hybridization; S – serology; seq – sequencing; * – captive wild.

Taxa diagnosed (genotype)	Host (scientific name)	Country	Substrate	Techniques	Reference
Psittaciformes					
Encephalitozoon	Blue-masked lovebird (*Agapornis personatus*)	USA*	Tissue	M	Kemp and Kluge 1975
Encephalitozoon	Double yellow-headed Amazon parrot (*Amazona ochrocephala*)	USA*	Tissue	M	Poonacha et al., 1985
E. hellem	Budgerigar (*Melopsittacus undulatus*)	USA*	Tissue	M + PCR	Black et al., 1997
E. hellem	Eclectus parrots (*Eclectus roratus*)	USA*	Tissue	M + PCR	Pulparampil et al., 1998
E. hellem	Peach-faced lovebird *(Agapornis roseicollis)*	USA*	Faeces	M + IF + PCR	Snowden et al., 2000
E. hellem	Umbrella cockatoo (*Cacatua alba*)	USA*	Conjunctival epithelium	M + PCR	Phalen et al., 2006
E. hellem (I)	Yellow-streaked lory (*Chalcopsitta scintillata*)	Switzerland* caught in the wild in Indonesia	Intestinal content	PCR/seq	Suter et al., 1998; Mathis et al., 1999
E. hellem (I)	Lovebirds (*Agapornis* spp.)	USA*	Faeces	M + culture + PCR/seq	Barton et al., 2003
E. hellem	Galah (*Eolophus roseicapillus*); Superb parrot *Polytelis swainsonii*	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A)	Festive amazon (*Amazona festiva*); Yellow-crowned amazon (*Amazona ochrocephala*); White cockatoo (*Cacatua alba*); Little corella (*Cacatua sanguinea*); Elegant parrot (*Neophema elegans*); Red-rumped parrot (*Psephotus haematonotus*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. cuniculi	Mealy amazon (*Amazona farinosa*); Tucumán amazon (*Amazona tucumana*); Red-crowned amazon (*Amazona viridigenalis*); Bronze-winged parrot (*Pionus chalcopterus*); Scaly-headed parrot (*Pionus maximiliani*); Dusky parrot (*Pionus fuscus*); Major Mitchell's Cockatoos (*Cacatua leadbeateri*); Green rosella (*Platycercus caledonicus*); Parakeets (*Pyrrhura* sp.); Monk parakeet (*Myiopsitta monachus*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. cuniculi (I)	Solomons cockatoos (*Cacatua goffini*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. cuniculi (II)	Red-fan parrot (*Deroptyus accipitrinus*); Red-crowned parakeet (*Cyanoramphus novaezelandia*); Senegal parrot (*Poicephalus senegalus*); African grey parrot (*Psittacus erithacus*); Crimson rosella (*Platycercus elegans*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. cuniculi (III)	Cockateel (*Nympicus hollandicus*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem, *E. cuniculi* (I + II)	Fischer's lovebird (*Agapornis fischeri*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A), *E. cuniculi* (I + II)	Rosy-faced lovebirds (*Agapornis roseicollis*); Rose-ringed parakeet (*Psittacula krameri*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem(1A), *E. cuniculi* (I)	Yellow-collared lovebirds (*Agapornis* personata)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (2C), *E. cuniculi*	Red-lored amazon (*Amazona autumnalis*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A), *E. cuniculi* (II)	Budgerigar (*Melopsittacus undulates*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A), *E. cuniculi*	Australian ringneck (*Barnardius zonarius*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. cuniculi (II, III)	Cockatiel (*Nymphicus hollandicus*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A), *E. cuniculi* (II)	Turquoise parrot (*Neophema pulchella*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A), *E. cuniculi* (I + II)	Eastern rosella (*Platycercus eximius*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A, 2C), *E. cuniculi* (II)	Budgerigars (*Melopsittacus undulatus*)	Czech Republic*	Tissue, faeces	PCR/RFLP	Sak et al., 2010
E. hellem (1A, 2B), *E. cuniculi* (II)	Parrots: African grey parrot (*Psittacus erithacus*); Blue-streaked lory (*Eos reticulata*); Chestnut-fronted macaw (*Ara severus*); Eclectus parrot (*Eclectus roratus*); Green-cheeked parakeet (*Pyrrhura molinae*); Red-shouldered macaw (*Diopsittaca nobilis*); Rose-ringed parakeet (*Psittacula krameri*)	South Korea*	Faeces	PCR/RFLP	Lee et al., 2011
E. hellem (1A)	Blue-fronted parrot (*Amazona aestival*); Mealy parrot (*Amazona farinose*); Peach-fronted parakeet (*Aratinga aurea*); Scaly headed parrot (*Pionus maximiliani)*; Budgerigar (*Melopsittacus undulates*)	Brazil confiscated (illegal trafficking)	Faeces	M + PCR/seq	Lallo et al., 2012b
E. hellem (2C)	Blue-and-yellow macaw (*Ara ararauna*); Blue-headed parrot (*Pionus menstruus*)	Brazil confiscated (illegal trafficking)	Faeces	M + PCR/seq	Lallo et al., 2012b
Apodiformes					
E. hellem (I)	Hummingbirds (*Calypte anna; Archilochus alexandri; Selasporus sasin*)	USA (migratory birds in rescue facility)	Tissue, faeces	M + PCR/seq	Snowden et al., 2001

Table 1 (*continued*)

Taxa diagnosed (genotype)	Host (scientific name)	Country	Substrate	Techniques	Reference
Passeriformes					
E. hellem	Gouldian finch (*Erythrura gouldiae*)	USA*	Tissue	M + PCR	Carlisle et al., 2002
E. hellem	Carrion crow (*Corvus corone*)	Poland	Faeces	M + FISH	Słodkowicz-Kowalska et al., 2006
E. hellem	Greater blue-eared starling (*Lamprotornis chalybaeus*); Java sparrow (*Padda oryzivora*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. cuniculi (II)	Red-billed firefinch (*Lagonosticta senegala*); Brahminy starling (*Temenuchus pagodarum*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A), *E. cuniculi* (I + II)	Atlantic canary (*Serinus canaria*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem, *E. cuniculi* (II)	Zebra finch (*Taeniopygia guttata*)	Czech Republic*	Faeces	PCR/RFLP	Kašičková et al., 2009
E. hellem (1A)	Grassland yellow-finch (*Sicalis luteola*)	Brazil confiscated (illegal trafficking)	Faeces	M + PCR/seq	Lallo et al., 2012b
E. hellem (2C)	Saffron finch (*Sicalis flaveola*)	Brazil confiscated (illegal trafficking)	Faeces	M + PCR/seq	Lallo et al., 2012b
E. hellem (1A)	Double-collared seedeater (*Sporophila caerulescens*); Chopi blackbird (*Gnorimopsar chopi*)	Brazil confiscated (illegal trafficking)	Faeces	M + PCR/seq	Lallo et al., 2012b
Anseriformes					
E. hellem	Mallard duck (*Anas platyrhynchos*); Greyleg goose (*Anser anser*); Mute swan (*Cygnus olor*); Black-necked swan (*Cygnus melancoryphus*); Black swan (*Cygnus atratus*); Coscoroba swan (*Coscoroba coscoroba*)	Poland	Faeces	M + FISH	Słodkowicz-Kowalska et al., 2006
Gruiformes					
E. hellem	Black-crowned crane (*Balearica pavonina*)	Poland*	Faeces	M + FISH	Słodkowicz-Kowalska et al., 2006
Columbiformes					
E. hellem	Nicobar pigeon(*Caloenas nicobarica*)	Poland*	Faeces	M + FISH	Słodkowicz-Kowalska et al., 2006
Suliformes					
E. cuniculi (I)	Great cormorant (*Phalacrocorax carbo*)	Slovakia	Faeces	M + PCR/seq	Malčeková et al., 2013
Podicipediformes					
E. cuniculi (I)	Great crested grebe (*Podiceps cristatus*)	Slovakia	Faeces	M + PCR/seq	Malčeková et al., 2013
Ciconiiformes					
E. cuniculi (I)	White stork (*Ciconia ciconia*)	Slovakia	Faeces	M + PCR/seq	Malčeková et al., 2013
Struthioniformes					
E. intestinalis	Ostrich (*Struthio camelus*)	Spain (farmed)	Faeces	M + PCR	Galvan-Diaz et al., 2014
E. hellem	Ostrich (*Struthio camelus*)	USA (farmed)	Tissue	M + PCR	Snowden and Logan 1999
Falconiformes					
E. cuniculi (II)	Gyrfalcon (*Falco rusticolus*)	Slovakia*	Faeces	M + PCR/seq	Malčeková et al., 2011

2.1.3. *Encephalitozoon intestinalis*

E. intestinalis is the most prevalent *Encephalitozoon* species in humans and occurs worldwide. It also has been shown to occur in several, predominantly domestic, mammalian species (e.g. goat, pig, cattle, dog, donkey or gorilla). Zoonotic transmission was proposed to be an important source in human infections (Bornay-Llinares et al., 1998; Graczyk et al., 2002; Didier, 2005; Malčeková et al., 2010). In Slovakia especially domesticated pigs were the animals most often infected, with prevalences of 51% or more (Valenčáková et al., 2006; Malčeková et al., 2010). In birds *E. intestinalis* has only been reported sporadically (Table 1). Genotypic variations in *E. intestinalis* were demonstrated (Galvan et al., 2013) but have not been applied to broader surveys.

2.2. *Diagnosis of Encephalitozoon spp.*

Materials that can be used for microsporidial diagnosis are tissue samples, fluids such as urin as well as faeces and serum (Garcia, 2002). When detecting spores in faeces only it cannot be excluded that these pathogens were just passaged in the gastrointestinal tract, e.g. via ingestion of infected mice (Bornay-Llinares et al., 1998). However, long term shedding of spores indicates infection (Sak et al., 2010).

Microscopical, molecular and serological methods are established for the detection of Microsporidia. Microscopy in combination with staining (e.g. Chromotrope 2R or fluorescence staining) allows to detect Microsporidia but not to differentiate species (Garcia, 2002). Whereas electron microscopy can be used for species detection (Garcia, 2002). Also detection of antibodies by serological techniques (e.g. indirect immunofluorescent-antibody testing (IFAT), enzyme-linked immunosorbent assay (ELISA), Western blotting; direct agglutination test (DAT)) is species specific (Garcia, 2002). Serological tests have been primarily established for detection of *E. cuniculi* and IFAT and ELISA are routinely used for

Table 2
Encephalitozoon spp. identified in non-human Primates. PCR – polymerase chain reaction; H – histology; M – microscopy; IF – immunofluorescence; FISH – fluorescent in situ hybridization; S – serology; seq – sequencing; * – captive wild.

Taxa diagnosed (genotype)	Host (scientific name)	Country	Substrate	Techniques	Reference
Encephalitozoon sp.	Squirrel monkey *(Saimiri sciureus)*	USA*	Tissue	H + M	Anver et al., 1972
Encephalitozoon sp.	Squirrel monkey *(Saimiri sciureus)*	USA*	Tissue	H	Brown et al., 1972
Encephalitozoon sp.	South American titi monkey (*Callicebus moloch cupreus*)	N/A*	N/A	H + M	Seibold and Fussell 1973
Encephalitozoon sp.	Squirrel monkey (*Saimiri sciureus)*	USA*	Tissue	H	Zeman and Baskin 1985
E. intestinalis	Mountain gorilla (*Gorilla b. beringei*)	Uganda	Faeces	M + PCR + FISH	Graczyk et al., 2002
E. cuniculi (III)	Emperor tamarin (*Saguinus imperator*)	Switzerland*	Tissue	M + IF + PCR/seq	Guscetti et al., 2003
E. cuniculi (III)	Cotton-top tamarin (*Saguinus oedipus*)	Germany*	Blood, tissue	M + PCR/seq	Reetz et al., 2004
E. cuniculi (III)	Cotton-top tamarin (*Saguinus oedipus*) Emperor tamarin (*Saguinus imperator*)	USA*	Tissue	M + S + PCR/seq	Juan-Salles et al., 2006
E. cuniculi (III)	Squirrel monkey *(Saimiri sciureus)*	Japan*	Tissue	PCR/seq	Asakura et al., 2006
E. cuniculi	Ring tailed lemur (*Lemur catta*)	USA*	Blood	S	Yabsley et al., 2007
E. cuniculi (II)	Goeldi's monkey (*Callimico goeldii*)	USA*	Vessels	H + PCR/seq	Davis et al., 2008
E. cuniculi (I)	Bonobo (*Pan paniscus*)	UK*; Germany*	Faeces	PCR/seq	Sak et al., 2011b
E. cuniculi (I, II), *E. hellem* (1A)	Common chimpanzee (*Pan troglodytes*)	Kenya*; Cameroon*	Faeces	PCR/seq	Sak et al., 2011b
E. cuniculi (I)	Common chimpanzee (*Pan troglodytes*)	Germany*; Spain*; Slovakia*; Ireland*; Czech Republic*	Faeces	PCR/seq	Sak et al., 2011b
E. cuniculi (I)	Western gorilla (*Gorilla g. gorilla*)	Cameroon	Faeces	PCR/seq	Sak et al., 2011b
E. cuniculi (I)	Western gorilla (*Gorilla g. gorilla*)	France*; Germany*; Poland*	Faeces	PCR/seq	Sak et al., 2011b
E. intestinalis	Red ruffed lemur (*Varecia rubra*); Ring tailed lemur (*Lemur catta*)	Poland*	Faeces	M + FISH + PCR	Słodkowicz-Kowalska et al., 2012
E. cuniculi (I, II)	Western gorilla (*Gorilla g. gorilla*)	Central African Republic	Faeces	PCR/seq	Sak et al., 2013
E. cuniculi (I, II)	Mountain gorilla (*Gorilla b. beringei*)	Rwanda	Faeces	PCR/seq	Sak et al., 2014
E. hellem	Moustached monkeys (*Cercocebus cephus*); Agile mangabey (*Cercocebus agilis*); Common chimpanzee (*Pan troglodytes*); Bonobo (*Pan paniscus*); Western gorilla (*Gorilla g. gorilla)*	Cameroon	Faeces	PCR/seq	Butel et al., 2015

detection of this pathogen in rabbits where they are considered to be the most important diagnostic tool (Künzel and Joachim, 2010). IFAT has been shown to be a sensitive and specific test for the detection of *E. cuniculi* in cats (Künzel et al., 2014). The DAT was also described to be a useful test for detection of *E. cuniculi* in animals but might need some refinement (Meredith et al., 2015). For some species, however, serology is not a reliable technique yet (Garcia, 2002; Mathis et al., 2005). In addition these tests cannot distinguish between an active and past infection. The ability of detecting past infections however is also an advantage of serology and makes it a useful tool to access overall prevalence.

The Fluorescence in situ hybridization technique (FISH) is a fluorescence microscopy method targeting rRNA and allows simultaneous identification of *Encephalitozoon* spores to the species level (Słodkowicz-Kowalska et al., 2006).

PCR is a highly sensitive and specific method. If followed by sequencing or restriction fragment length polymorphism techniques it allows to detect strains and genotypes. These PCR methods with subsequent genotyping yield valuable results for epidemiological studies as differentiation to the subspecies level allows assumptions on host specificity, origin, transmission pathways and spreading dynamics of the pathogen (Xiao et al., 2001;

Table 3
Encephalitozoon spp. identified in wild Lagomorpha. PCR – polymerase chain reaction; H – histology; S – serology.

Taxa diagnosed (genotype)	Host (scientific name)	Country	Substrate	Techniques	Reference
E. cuniculi	European rabbit (*Oryctolagus cuniculus*)	UK	N/A	N/A	Wilson 1979
E. cuniculi	European rabbit (*Oryctolagus cuniculus*)	France	–	S	Chalupsky et al., 1990
E. cuniculi	European rabbit (*Oryctolagus cuniculus*)	Australia	Tissue	S, culture	Thomas et al., 1997
E. intestinalis, E. hellem	European brown hare (*Lepus europaeus*)	Belgium	Tissue	H, PCR	De Bosschere et al., 2007
E. cuniculi	Cottontail rabbit (*Sylvilagus floridanus*)	Italy	Tissue	PCR	Zanet et al., 2013
E. cuniculi	European hare (*Lepus europaeus*)	Czech Republic, Austria, Slovak Republic	–	S	Bártová et al., 2015

Table 4
Encephalitozoon spp. identified in wild Rodentia. PCR – polymerase chain reaction; H – histology; M – Microscopy; S – serology; seq – sequencing; * – captive wild.

Taxa diagnosed (genotype)	Host (scientific name)	Country	Substrate	Techniques	Reference
E. cuniculi	Muskrat (*Ondatra zibethica*)	N/A	Tissue	H	Wobester and Schuh 1979
Encephalitozoon sp.	Arctic lemming (*Dicrostonyx torquatus*)	USA*	Tissue	H	Cutlip and Beall 1989, Cutlip and Dennis 1993
E. cuniculi	House mice (*Mus musculus*); Wood mice (*Apodemus sylvaticus*)	Iceland	Tissue	M + S	Hersteinsson et al., 1993
E. cuniculi (II)	Brown rat (*Rattus norvegicus*)	Switzerland	Tissue	S, PCR/seq, culture	Müller-Doblies et al., 2002
E. cuniculi	Common vole (*Microtus arvalis*); Water vole (*Arvicola terrestris*)	Austria	Tissue	PCR	Fuehrer et al., 2010
E. hellem (1A), *E. cuniculi* (I), *E. cuniculi* (II)	Eastern European house mouse (*Mus musculus musculus*)	Czech Republic, Germany	Tissue	PCR/seq	Sak et al., 2011a
E. hellem (1A), *E. cuniculi* (I, II)	Western European house mouse (*M. m. domesticus*)	Czech Republic, Germany	Tissue	PCR/seq	Sak et al., 2011a
E. cuniculi (I, III), *E. hellem*, *E. intestinalis*	Wood mouse (*Apodemus specious*)	Japan	Tissue	PCR/sek	Tsukada et al., 2013
E. cuniculi (I), *E. hellem*	Small Japanese field mouse (*Apodemus argenteus*)	Japan	Tissue	PCR/seq	Tsukada et al., 2013
E. cuniculi (I, III), *E. hellem*, *E. intestinalis*	Japanese grass vole (*Microtus montebelli*)	Japan	Tissue	PCR/seq	Tsukada et al., 2013
E. cuniculi (III)/seq	Steppe lemmings (*Lagurus lagurus*)	Czech Republic*	Tissue	H + PCR	Hofmannová et al., 2014
Encephalitozoon sp.	Wild rat (species not determined)	Egypt	–	S	Abu-Akkada et al., 2015
E. cuniculi, *E. intestinalis*	House mouse (*Mus musculus*)	Slovakia	Faeces	PCR	Danišová et al., 2015
Encephalitozoon sp.	Bank vole (*Myodes glareolus*); Field vole (*Microtus agrestis*); Wood mouse (*Apodemus specious*)	UK	–	S	Meredith et al., 2015

Table 5
Encephalitozoon spp. identified in wild Carnivora. PCR – polymerase chain reaction; M – microscopy; S – serology; seq – sequencing; * – captive wild.

Taxa diagnosed (genotype)	Host (scientific name)	Country	Substrate	Techniques	Reference
E. cuniculi	Red fox (*Vulpes vulpes*)	UK	N/A	N/A	Wilson 1979
Encephalitozoon sp.	Mink	Norway (farmed)	Tissue	M	Bjerkas and Nesland 1987
E. cuniculi	Wild dogs (*Lycaon pictus*)	South Africa*	Tissue	M	Van Heerden et al., 1989
E. cuniculi	Arctic fox (*Alopex lagopus*); Feral mink (*Mustela vison*)	Iceland	Tissue	M + S	Hersteinsson et al., 1993
E. cuniculi	European otter (*Lutra lutra*); Martens (*Martes* sp.)	Czech Republic	Brain	PCR	Hůrková and Modrý 2006
E. cuniculi, *E. intestinalis*	Red fox (*Vulpes vulpes*)	Ireland	Tissue	M + PCR	Murphy et al., 2007
E. cuniculi, *E. hellem*, *E. intestinalis*	Coati (*Nasua nasua*)	Brazil	Faeces, urine	M + PCR	Lallo et al., 2012a
E. cuniculi	Red fox (*Vulpes vulpes*)	UK	–	S	Meredith et al., 2015
Encephalitozoon sp.	South American fur seal (*Arctocephalus australis*)	Chile	Tissue	H	Seguel et al., 2015
E. cuniculi (III)	Snow leopard (*Panthera uncia*)	Austria*	Eye lens	M + PCR/seq	Scurrell et al., 2015

Table 6
Encephalitozoon spp. identified in wild Artiodactyla. PCR – polymerase chain reaction.

Taxa diagnosed (genotype)	Host (scientific name)	Country	Substrate	Techniques	Reference
E. cuniculi (I, II)	Cape buffalo (*Syncerus caffer*)	Central African Republic	Faeces	PCR/seq	Sak et al., 2013
E. cuniculi (I)	Duiker (*Cephalophus* spp.)	Central African Republic	Faeces	PCR/seq	Sak et al., 2013
E. cuniculi (II)	Wild boar (*Sus scrofa*)	Austria	Faeces	PCR/seq	Němejc et al., 2014
E. cuniculi (I, II)	Wild boar (*Sus scrofa*)	Czech Republic	Faeces	PCR/seq	Němejc et al., 2014
E. cuniculi (II)	Wild boar (*Sus scrofa*)	Slovakia	Faeces	PCR/seq	Němejc et al., 2014

Haro et al., 2005; Mathis et al., 2005; Ghosh and Weiss, 2009).

2.3. Infection routes

The main sources of infection with microsporidia and for zoonotic transmission are in most cases unclear. Microsporidia produce spores which are excreted via faeces, sputum or urine and have a long lifespan in the environment (Li et al., 2003; Sinski, 2003). Besides oral uptake, it is suggested that inhalation can lead to infection as *Encephalitozoon* spp. are present in lung tissue and lung secretion (Cox et al., 1979; Rinder, 2004; Didier et al., 2004; Didier and Weiss, 2006; Graczyk et al., 2007). Successful experimental intranasal transmission was described in mice (Nelson, 1967). Transplacental transmission is described in rabbits and canids (Cox et al., 1979; Baneux and Pognan, 2003). As a similar mechanism, transovarial transmission of microsporidia was described for birds (Reetz, 1994). *Encephalitozoon* was also found in the salivary glands of ticks (Ribeiro and Guimaraes, 1998), but until now the significance of Arthropoda as vectors of microsporidia is unknown (Didier, 2005). Human-to-human transmission e.g. through smear infections in case of keratoconjunctivitis or through organ transplantation has been described and sexual transmission is considered likely to occur (Didier et al., 2004; Didier, 2005; Hocevar et al., 2014).

3. Orders of wild animals infected with *Encephalitozoon*

3.1. *Encephalitozoon* in wild birds

Several infections caused by *Encephalitozoon* spp. have been described in wild birds (Table 1) and these seem to be infected more commonly than mammals (Słodkowicz-Kowalska, 2009). Besides *Enterocytozoon* spp. (Haro et al., 2006b; Lobo et al., 2006; Bart et al., 2008), *E. hellem* is a highly prevalent microsporidian species of birds (Słodkowicz-Kowalska et al., 2006; Malčeková et al., 2013). However, in most studies only one of several genera of microsporidia was tested for so that a direct comparison is not feasible. *E. cuniculi* and *E. intestinalis* have also been detected in the faeces of birds by molecular analysis, albeit with lower prevalence. Although birds are most probably not the main host of *E. cuniculi* (Kašičková et al., 2009) in some studies this species was the most prevalent in exotic pet birds and in pigeons and such birds therefore seem to constitute an additional reservoir for *E. cuniculi*, too (Haro et al., 2006b; Lobo et al., 2006; Bart et al., 2008).

3.2. Encephalitozoon in wild mammals

In the Class Mammalia several orders (Rodentia, Lagomorpha, Primates, Artyodactyla, Soricomorpha, Chiroptera, Carnivora) were detected with *Encephalitozoon* and are listed in Tables 1–6 (Soricomorpha and Chiroptera are not shown in the tables). Some special features will be highlighted in the following text:

3.2.1. Encephalitozoon in the order primates

In great apes the geographical distribution of different *Encephalitozoon* species seems to vary so location of affected animals seems to determine which species of pathogen is present (Table 1). While Western lowland gorillas from a Central African Republican free-ranging population, kept in a sanctuary in Cameroon and in various zoos in Poland, Germany and France, were positive for the presence of *E. cuniculi* genotype I and II (Sak et al., 2011b), only *E. hellem* was detected in three free-ranging animals from Cameroon (Butel et al., 2015). Similarly, in bonobos (*Pan paniscus*) and common chimpanzees (*Pan troglodytes*) screened by Butel et al. (2015) from Cameroon, only *E. hellem* was detected, while the same species kept in sanctuaries in Kenya and Cameroon and various zoos in UK, Germany, Spain, Slovakia, Ireland and the Czech Republic was mostly positive for *E. cuniculi* genotype I and II, *E. hellem* was detected in two cases only (Sak et al., 2011b). This demonstrates the ubiquitous character and low host specificity of this genus.

3.2.2. Encephalitozoon in the suborder Lagomorpha

Despite the abundance and importance of encephalitozoonosis in domestic rabbits (*Oryctolagus cuniculus*) (Künzel and Joachim, 2010) reports of this infection in wild lagomorphs are rather limited (Table 3). *Encephalitozoon* - positive wild rabbits were described from France with a comparatively low prevalence of 3.9% (Chalupský et al., 1990) compared to domestic populations. Except for a single description of an *E. cuniculi* infected wild rabbit by Wilson (1979), no infections in the UK and in Germany in wild populations could be demonstrated so far (Cox et al., 1980; Bose et al., 2015). However, prevalence in captive rabbits in these countries were quite high (Keeble and Shaw, 2006; Hein et al., 2014). In an early prevalence study, 880 wild rabbits (*O. cuniculus*) from Australia (Victoria) and New Zealand as well as 46 hares (*Lepus europaeus*) form Australia tested negative for *E. cuniculi* by serology although susceptibility to the parasite was demonstrated by experimental infections (Cox and Ross, 1980). This may be because housed animals are much more exposed to spores especially in overcrowded conditions (Cox and Ross, 1980). However, in a study from Western Australia, a prevalence of 25% for *E. cuniculi* was detected in wild rabbits (Thomas et al., 1997), indicating a possible spread in the wild population.

In a recent study in the Czech Republic, Austria and the Slovak Republic 1.42% of European hares (*Lepus europaeus*) were tested positive for *E. cuniculi* by serology (Bártová et al., 2015).

3.2.3. Encephalitozoon in the suborder Rodentia

Rodents comprise about 40% of the mammalian diversity and occupy a wide range of habitats (Musser and Carleton, 2005). They are generally considered an important reservoir of zoonotic pathogens including microsporidia (Begon, 2003; Mathis et al., 2005). Although mice and rats are widespread, our current knowledge on the occurrence, prevalence and pathogenicity of *Encephalitozoon* spp. in wild rodents is very limited (Table 4). In Europe as well as in Japan up to 34% house mice and up to 19% of voles were tested positive for *Encephalitozoon* spp. (Fuehrer et al., 2010; Sak et al., 2011a; Tsukada et al., 2013; Danišová et al., 2015).

3.2.4. Encephalitozoon in the order Carnivora

While examination of wild canids from Iceland showed that 11% of the examined arctic foxes (*Alopex lagopus*) had positive antibody titres against *E. cuniculi* (Hersteinsson et al., 1993), Åkerstedt and Kapel (2003) did not detect *E. cuniculi* infections in arctic foxes in Greenland and suggested that these differences to the study in Iceland were due to different feeding habits. Unlike foxes in Iceland, mice are not part of the diet of foxes in Greenland.

In the UK, red foxes had higher seroprevalences than rodents from the same area, namely 52%. They might therefore play an important role as a reservoir for microsporidia in the sylvatic cycle and could be suitable sentinel animals (Meredith et al., 2015).

3.2.5. Encephalitozoon in the suborder Soricomorpha

The taxon most closely related to the Primates is not very well studied for infections of *Encephalitozoon* spp. *E. cuniculi* genotype I and *E. intestinalis* were detected by PCR in Japanese shrew mole (*Urotrichus talpoides*) in Japan. One of two examined Dsinezumi shrews (*Crocidura dsinezumi*) was positive for *E. hellem* in the same study (Tsukada et al., 2013).

3.2.6. Encephalitozoon in the order Chiroptera

Despite Chiroptera representing about 20% of the mammalian fauna, only one case of *E. hellem* (based on sequencing of the SSUrDNA locus) in a captive Egyptian fruit bat (*Rousettus aegyptiacus*) was reported.

4. Medical implications

4.1. Human health

4.1.1. Encephalitozoonosis in humans

Microsporidia are common causative agents of diarrhea in HIV infected patients worldwide. Besides the intestine they can infect any other organ of the human body as well and might cause severe live threatening systemic diseases. Incidence of clinical cases decreased in areas where widespread application of antiretroviral therapy was initiated. Besides AIDS other immune compromising conditions can go along with clinical microsporidiosis. It is supposed that in addition to a possible acute infection disease could also be due to a reactivation of a persistent infection under immune-compromising conditions. *Encephalitozoon* is increasingly recognized to occur in non immuncompromised individuals. The significance of this observation is not fully clear and while most infections might be asymptomatic some cases of diarrhea of unknown aetiology might be caused by microsporidial infection (Didier and Weiss, 2011; Didier et al., 2004; Mathis et al., 2005; Didier and Weiss, 2006).

4.1.2. Sources of infection and zoonotic transmission

A wide range of animals are infected with microsporidia which are infective for humans as well. Zoonotic transmission therefore seems likely (McCully et al., 1978; Didier, 2005; Snowden et al., 2009). Zoonotic transmission through wildlife might occur irrespective of the immediate presence of animals and rather through contamination of the environment with spores shed by faeces or urine.

Microsporidial spores have been detected in various water sources and as their spores are very viable in water, water is considered to play an important role in transmission of microsporidia (Dowd et al., 1998; Fournier et al., 2000; Coupe et al., 2006; Izquierdo et al., 2011; Guo et al., 2014). Indeed contact to water is a frequently identified risk factors for the infection of humans with microsporidia (Hutin et al., 1998; Cotte et al., 1999; Didier et al., 2004; Mathis et al., 2005). A waterborne outbreak of microsporidia was suggested in a study were people infected with microsporidia all lived in an area with the same water supply (Cotte et al., 1999). In this study, however, water was not tested for microsporidial contamination so that a waterborne outbreak could not be proven. Another substrate shown to be contaminated with microsporidia is soil (Dado et al., 2012; Kim et al., 2015). Lack of sanitation has been identified as a risk factor (Halánová et al., 2013) and in a recent study it was observed that municipality solid waste workers had a high prevalence of microsporidial infections with about 20% of workers being infected (Abd El Wahab et al., 2015). Fruits, leaves and juices have been shown to be contaminated by microsporidia as well (Calvo et al., 2004; Mossallam, 2010) and a foodborne outbreak of encephalitozoonosis associated with cucumber has been described in Sweden (Decraene et al., 2012). Further proposed risk factors are age (possibly elderly and children are more commonly infected) and travelling (Tumwine et al., 2005; Didier and Weiss, 2006; Halánová et al., 2013).

The extent to which animals contribute to contamination of the environment still is unknown and in the following some pathways that might be crucial for zoonotic transmission are discussed:

Infections of wild birds are of special epidemiologic importance as these hosts can spread zoonotic agents, including microsporidia, via different substrates (e.g. air, soil or water) and across long distances (Graczyk et al., 2008). This also applies to domestic free-ranging birds, especially pigeons which have frequently been shown to be infected with zoonotic microsporidia including all three *Encephalitozoon* spp. (Haro et al., 2006a; Graczyk et al., 2007; Bart et al., 2008; Pirestani et al., 2013). Microsporidal spores can be aerosolized, e.g. when surfaces contaminated with pigeon faeces (and spores) are pressure-cleaned. That way spores might get inhaled or swallowed by cleaning staff or people nearby (Graczyk et al., 2007). Surface water may also become contaminated with faeces runoff during periods of rain. Exposure to infected urban park pigeons might thus lead to zoonotic transmission of microsporidia (Haro et al., 2005). Especially waterfowl may be a major source of contamination of surface waters as they show very high infection rates with potentially zoonotic microsporidia (Graczyk et al., 2008; Malčeková et al., 2013). Furthermore, aquatic birds frequently defecate into water and usually have unlimited access to surface water used for drinking water production. As otters and minks live close to water, they could also be an important source of waterborne infections. Measures to protect drinking and recreational water resources might therefore be important in preventing waterborne human infections (Graczyk et al., 2008).

In Brazil, coatis were infected at high rates (Table 5) and they might be a relevant reservoir for zoonotic microsporidia in this area, especially in public parks that become contaminated by animals shedding spores, as coatis live in close proximity to humans and sometimes even enter houses in search for food (Lallo et al., 2012a). Similar considerations apply for foxes that have been observed to shed a considerable amount of spores. Through their ubiquitous presence rodents might be an important source for potential zoonotic transmission as well.

Besides the environmental contamination by free-living wild animals, direct transmission through contact to captive wild animals might pose a specific risk.

4.2. Animal health

4.2.1. Encephalitozoonosis in wildlife

There is very limited information on encephalitozoonosis of free living wild animals.

We just give some examples of disease that could be observed in wild animals. Most cases described in the following were observed in captive wild or free living animals recently caught.

4.2.1.1. Encephalitozoonosis in wild birds. Several case reports of encephalitozoonosis in captive wild birds are described. Diseased animals showed keratoconjunctivitis or frequently fatal systemic disease e.g. with lesions in several organs such as the lungs, intestine, liver, spleen or kidney (Poonacha et al., 1985; Black et al., 1997; Snowden and Logan, 1999; Carlisle et al., 2002; Phalen et al., 2006). Subsequent studies on larger populations showed that asymptomatic infections in captive wild birds are widespread (Barton et al., 2003; Kašičková et al., 2009; Sak et al., 2010; Lee et al., 2011). However, the impact of infections on the health of free-living wild birds is largely unknown. A yellow-streaked lori (*Chalcopsitta scintillata*) that was caught from the wild in Indonesia and died soon after in poor health state tested positive for *E. hellem* (Suter et al., 1998).

In wild hummingbirds kept in a rehabilitation facility, *E. hellem* genotype 1 was associated with enteritis, especially in nestlings, while older birds were more likely to harbour inapparent infections. *E. cuniculi* is known to cause ocular cataracts in blue foxes; felids and in dogs (Arnesen and Nordstoga, 1977; Benz et al., 2011; Nell et al., 2015), it was also suspected to be a possible cause of eye lens cataracts in wild birds, as *E. cuniculi* could be detected in the lens of an owl (with no obvious impairment of the eyes) and by PCR in the phacoemulsified lens of a captive saker falcon chick with cataractous lenses (Hinney et al., 2015). Coupled with a loss of vision, e.g. due to cataract, the infection might influence the bird's behaviour (such as problems with hunting for prey).

4.2.1.2. Encephalitozoonosis in primates. In non-human primates lethal infection with *E. cuniculi* were described with genotype II and III (Davis et al., 2008; Juan-Salles et al., 2006; Reetz et al., 2004).

4.2.1.3. Encephalitozoonosis in Chiroptera. In Chiroptera histopathological examination revealed disseminated microsporidiosis with pronounced lesions particularly in the urogenital tract and liver (Childs-Sanford et al., 2006).

4.2.1.4. Encephalitozoonosis in wild carnivores. Susceptibility of farmed arctic foxes is documented since the early cases of severe systemic diseases with brain and kidney as predilection organs caused by *E. cuniculi* genotype II with high mortality (Mohn, 1982; Henriksen, 1986; Persin and Dousek, 1986; Åkerstedt et al., 2002; Martino et al., 2004; Meng et al., 2014). Captive arctic foxes are known to be very susceptible to encephalitozoonosis and Åkerstedt and Kapel (2003) further hypothesised that this might be due to the lack of contact of this host with the pathogen during evolution with implications for the development of an appropriate defence mechanism of their immune system. Red foxes usually do not show clinical signs of infection but are frequently infected with *Encephalitozoon* (Table 5).

4.2.2. Transmission paths in wildlife

In principle infection sources might be similar to those discussed for humans, namely contaminated water, soil and food (including prey). For some animals e.g. rabbits and carnivores transplacental transmission might be of importance and probably helps to maintain the pathogen within the population of a species (Hersteinsson et al., 1993; Cox et al., 1979; Baneux and Pognan, 2003).

In great apes, being endangered species, the anthropozoonotic transmission of human pathogens is of special concern, as humans and apes are closely related and thus susceptible for inter-species infections (Groves, 2005). Moreover, an increased anthropogenic impact on primate populations (through tourism and habituation) may result in changes in communities of their parasites, also in a direct exchange of parasites between humans and primates (Sak et al., 2011b). Indeed, infections with *Encephalitozoon* spp. that can also affect humans have been detected in great apes (Table 2). Graczyk et al. (2002) observed that humans and free-ranging mountain gorillas (*Gorilla beringei beringei*) in Uganda both harboured *E. intestinalis* infections. Close interactions between humans and non-human primates can create pathways for the transmission of zoonotic diseases in both directions.

5. Discussion

Encephalitozoonosis is substantially more than a rabbit's parasitosis. Quite the contrary, in many geographic regions wild rabbits do not seem to be important reservoirs of this infection in the wild. A large range of birds and wild mammals may act as hosts, many of them probably also as reservoirs for these pathogens with an ever increasing number of reports of new host species for all genotypes of *Encephalitozoon*. As observed in great apes, location of animals rather than host species may influence the species composition of microsporidia in the animal environment. This further confirms that the situation in captivity does not permit extrapolations on the dimension of natural infections in the wild.

Nevertheless, despite the lack of data for many species, differences in prevalence between the animal orders investigated so far are evident. *E. intestinalis* is comparatively rarely found in wildlife. While domestic pigs have been shown to be infected with *E. intestinalis* in high prevalences (Valenčáková et al., 2006; Malčeková et al., 2010), this does not seem to be the case for wild boar so far (Němejc et al., 2014). For this species, domestic animals rather than wildlife might constitute the most important reservoir for zoonotic transmission. Birds can be assumed to be the primary reservoir for *E. hellem*, while some but not all mammals are frequent carriers of *E. cuniculi*. Due to their abundance and close proximity to humans rodents and carnivores might be important carriers of *E. cuniculi*; however, they also constitute the groups that are most intensively studied.

Wildlife thus should be considered as possible source for zoonotic transmission of microsporidia of the genus *Encephalitozoon* (Didier et al., 2004; Didier, 2005; Mathis et al., 2005; Murphy et al., 2007). Conversely, humans entering wild animal habitats in search for food or land often bring their domestic animals with them which may harbour pathogens previously unknown to that area, posing a threat to indigenous species, especially endangered ones.

Disease caused by *Encephalitozoon* seems to be governed more by the immune status of the individual host than by the host species itself. Indeed, free-living animals were frequently observed to developed disease shortly after captivity, which may be related to stress and resulting immunosuppression (Mbyaya et al., 2009; Dickens et al., 2009). Thus, although *Encephalitozoon* infections are observed to be predominantly subclinical, they could be an important driver of selection during stressful events (Cox and Ross, 1980; Bose et al., 2015).

Due to the different methodologies applied in previous studies, no conclusion can be drawn regarding the geographic distribution of the different *Encephalitozoon* species. Studies in great apes have shown that geographical differences exist, but the extent and epidemiological consequence of this finding is unclear. Animals that have been shown to shed high amounts of spores might be useful sentinel animals to draw conclusion on environmental contamination.

To fully apprehend the importance of *Encephalitozoon* as a pathogen for wild and domestic animals as well as humans, future studies must be guided by appropriate methodologies to cover all *Encephalitozoon* species and known genotypes, and by selection of appropriate sentinel host species to receive meaningful information.

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