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Invited Review

Cryptosporidiosis and *Cryptosporidium* species in animals and humans: A thirty colour rainbow?

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ABSTRACT

Parasites of the genus *Cryptosporidium* (Apicomplexa) cause cryptosporidiosis in humans and animals worldwide. The species names used for *Cryptosporidium* spp. are confusing for parasitologists and even more so for non-specialists. Here, 30 named species of the genus *Cryptosporidium* are reviewed and proposed as valid. Molecular and experimental evidence suggests that humans and cattle are the hosts for 14 and 13 out of 30 named species, respectively. Two, four and eight named species are considered of major, moderate and minor public health significance, respectively. There are at least nine named species that are shared between humans and cattle. The aim of this review is to outline available species information together with the most commonly used genetic markers enabling the identification of named *Cryptosporidium* spp. Currently, 28 of 30 named species can be identified using the complete or partial ssrRNA, serving as a retrospective 'barcode'. Currently, the ssrRNA satisfies the implicit assumption that the reference databases used for comparison are sufficiently complete and applicable across the whole genus. However, due to unreliable annotation in public DNA repositories, the reference nucleotide entries and alignment of named *Cryptosporidium* spp. has been compiled. Despite its known limitations, ssrRNA remains the optimal marker for species identification.

1. Introduction

Cryptosporidium spp. cause significant diarrhoeal disease in humans and animals worldwide (Bouzid et al., 2013). The genus *Cryptosporidium* belongs to the phylum Apicomplexa, which includes other major pathogens of medical and veterinary importance such as *Plasmodium* spp. causing malaria, *Toxoplasma gondii* causing toxoplasmosis and *Eimeria* spp. causing coccidiosis. The intracellular parasites of the genus *Cryptosporidium* infect mammals, birds, reptiles and amphibians (Santín, 2013). Cryptosporidiosis is commonly a self-limiting disease in healthy hosts but represents a life-threatening disease in immuno-compromised and young individuals, for which there is no effective treatment (Bouzid et al., 2013).

Morphologically indistinguishable isolates of *Cryptosporidium* spp. are rather heterogeneous in their DNA sequences, and several of those that initially acquired a 'genotype' status were later recognised as distinct species (Plutzer and Karanis, 2009; Xiao, 2010; Chalmers and Katzer, 2013). The nomenclature used for *Cryptosporidium* spp. is complex and is confusing for parasitologists and even more so for non-specialists. Once a species name is introduced and is linked to a material, it becomes the international standard of reference (International Commission on Zoological Nomenclature, 1999). Because it is an international standard a set of rules is in place to maintain continuity and stability of the names. On the other hand, for 'genotypes' there are no rules for using, renaming or introducing new examples, hence allowing constant flux.

The use of stable nomenclature is needed to marry current and future research with the original published information on *Cryptosporidium* spp. Therefore, the aim of this review is to outline named species together with the most commonly used genetic marker enabling *Cryptosporidium* spp. identification. This review does not cover yet unnamed species, 'genotypes' and other variants and subtypes. Representative DNA entries have been compiled to enable species identification serving as a reference standard – 'barcode' – supplementing species descriptions.

2. The named species are only some colours of the rainbow: How many is enough?

In the last decade, the number of named species has grown steadily, with approximately one new named species per year, and 10 named species for 2004–2013. Currently, the total tally is 30 valid, named species (Table 1). This number appears to be a fair coverage of *Cryptosporidium* spp. from a medical and veterinary perspective. The species that have been named and recognised are the outcome of molecular surveys and experimental studies

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Table 1
Current summary of *Cryptosporidium* spp.

Species Number	Valid species name	Public health significance	Host range	Human	Cattle	Genotype designation
Species I	*C. muris* Tyzzer, 1907	Minor	MB	Yes		*C. muris* B genotype
Species II	*C. parvum* Tyzzer, 1912	Minor	M	(Yes)		Mouse I genotype
Species III	*C. meleagridis* Slavin, 1955 (syn. *C. tyzzeri* Levine, 1961)	Moderate	MB	Yes	(Yes)	
Species IV	*C. wrairi* Vetterling, Jervis, Merrill & Sprinz, 1971	None	M		(Yes)	
Species V	*C. agni* Barker & Carbonell, 1974 (syn. *C. xiaoi* Fayer & Santín, 2009)	None	M			*C. bovis*-like genotype
Species VI	*C. bovis* Barker & Carbonell, 1974	None	M		Yes	Bovine B genotype
Species VII	*C. cuniculus* Inman & Takeuchi, 1979	Moderate	M	Yes		Rabbit genotype
Species VIII	*C. felis* Iseki, 1979	Moderate	M	Yes	(Yes)	Cat genotype
Species IX	*C. serpentis* Levine, 1980	None	RM		(Yes)	
Species X	*C. nasoris* Hoover, Hoerr, Carlton, Hinsman & Ferguson, 1981	None	F			n/a
Species XI	*C. baileyi* Current, Upton & Haynes, 1986	None	B			
Species XII	*C. varanii* Pavlásek, Lávičková, Horák, Král & Král, 1995 (syn. *C. saurophilum* Koudela & Modrý, 1998)	None	R			Desert monitor genotype
Species XIII	*C. cichlidis* (Paperna & Vilenkin, 1996)	None	F			Piscine genotype 1
Species XIV	*C. reichenbachklinkei* (Paperna & Vilenkin, 1996)	None	F			Piscine genotype 2
Species XV	*C. galli* Pavlásek, 1999	None	B			Finch genotype
Species XVI	*C. andersoni* Lindsay, Upton, Owens, Morgan, Mead, & Blagburn, 2000	Minor	M	Yes	Yes	*C. muris* A genotype
Species XVII	*C. canis* Fayer, Trout, Xiao, Morgan, Lal & Dubey, 2001	Minor	M	Yes	(Yes)	Dog genotype
Species XVIII	*C. hominis* Morgan-Ryan, Fall, Ward, Hijjawi, Sulaiman, Fayer, Thompson, Olson, Lal & Xiao, 2002	Major	M	Yes	Yes	Human (I) genotype
Species XIX	*C. molnari* Alvarez-Pellitero & Sitjà-Bobadilla, 2002	None	F			
Species XX	*C. suis* Ryan, Monis, Enemark, Sulaiman, Samarasinghe, Read, Buddle, Robertson, Zhou, Thompson & Xiao, 2004	Minor	M	(Yes)	Yes	Pig genotype II
Species XXI	*C. scophthalmi* Alvarez-Pellitero, Quiroga, Sitjà-Bobadilla, Redondo, Palenzuela, Padrós, Vázquez & Nieto, 2004	None	F			n/a
Species XXII	*C. pestis* Šlapeta, 2006	Major	M	Yes	Yes	Bovine (II) genotype
Species XXIII	*C. fayeri* Ryan, Power & Xiao, 2008	Minor	M	(Yes)		Marsupial genotype I
Species XXIV	*C. ryanae* Fayer & Santín, Trout, 2008	None	M		Yes	Deer-like genotype
Species XXV	*C. fragile* Jirků, Valigurová, Koudela, Křížek, Modrý & Šlapeta, 2008	None	A			
Species XXVI	*C. macropodum* Power & Ryan, 2008	None	M			Marsupial genotype II
Species XXVII	*C. ducismarci* Traversa, 2010	None	R			
Species XXVIII	*C. ubiquitum* Fayer, Santín & Macarisin, 2010	Minor	M	Yes	Yes	Deer genotype
Species XXIX	*C. viatorum* Elwin, Hadfield, Robinson, Crouch & Chalmers, 2012	Moderate	M	Yes		
Species XXX	*C. scrofarum* Kváč, Kestřánová, Pinková, Květoňová, Kalinová, Wagnerová, Kotková, Vítovec, Ditrich, McEvoy, Stenger & Sak, 2013	Minor	M	(Yes)	(Yes)	Pig genotype II

Host range: M, mammal; B, bird; R, reptile; F, fish. n/a, not applicable because the species has not been characterised using any DNA signature. (Yes), indicates extremely rare or experimental evidence.

worldwide. However, in between the named species exists a great diversity of forms or genotypes that may or may not deserve specific status.

The validity of any species is based on a testable species concept that is applicable across the genus (Nadler and Leòn, 2011). The 10 species of *Cryptosporidium* named in the last decade were proposed as distinct based on their biological and genetic characteristics (Alvarez-Pellitero et al., 2004; Ryan et al., 2004b, 2008; Fayer et al., 2008, 2010; Elwin et al., 2012b; Kváč et al., 2013).

The principal parasitic attribute – host specificity – is universally applied across *Cryptosporidium* spp., but its reliability is ambiguous (Table 1). In fact, at least five of the 10 most recently named species have been detected in humans. Similarly, five of the 10 were shown to be experimentally infective for cattle. Not all are frequent parasites of either humans or cattle; rather the opposite. Recognition of common as opposed to rare events is only possible for these two hosts due to the enormous efforts directed towards this dataset, representing thousands of isolates analysed globally (Santín et al., 2004, 2008; Fayer et al., 2006b; Elwin et al., 2012a). The experimental evidence needs to be interpreted with caution because some experiments may represent unnatural contexts (Poulin and Keeney, 2008). Nevertheless, apparent parasite errors demonstrate the plasticity of these species and are recognised in an ecological concept known as "ecological fitting" (Agosta et al., 2010). The concept suggests that these known and experimental events or 'fits' are recent adaptations enabling the formation of species communities under changing environments (Agosta et al., 2010). These 'fits' are enabled opportunistically by the changing environment, e.g. proximity to a parasite reservoir. Otherwise specialist species with a relatively narrow host range such as *Cryptosporidium scrofarum*, *Cryptosporidium suis*, *Cryptosporidium fayeri*, *Cryptosporidium cuniculus* and *Cryptosporidium parvum* are found in humans, a host species with which they have no previous history of association (Xiao et al., 2002; Kváč et al., 2009; Waldron et al., 2010; Rašková et al., 2013). As opportunities for these events increase, the occurrence of an emerging infectious disease increases as well. An example of such is an outbreak of human cryptosporidiosis caused by *C. cuniculus* (Chalmers et al., 2009b). The origin of the *C. cuniculus* outbreak was resolved with relative ease, because rabbits are a reservoir of *C. cuniculus* (Robinson et al., 2010). A recently described species, *Cryptosporidium viatorum*, from humans most probably represents another such event but a reservoir is yet to be documented (Elwin et al., 2012b). Cataloguing and phylogenetic analyses of the genus *Cryptosporidium*, together with inference from host–parasite associations are valid approaches. The use of stable nomenclature is fundamental in pinpointing the origin of an emerging infectious disease.

Therefore, there is no definitive number of species names needed. The names are practical labels that enable scientific communication, e.g. *C. viatorum*, in the quest to identify its reservoir and epidemiology. More species will be named as the need arises