

Request of an opinion

Rejection of the name *Borrelia* gen. nov. and all proposed species comb. nov. placed therein. Request for an opinion.

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Abstract

Rejection (*nomen rejiciendum*) of the name *Borrelia* gen. nov. and all new combinations therein is being requested on grounds of risk to human health and patient safety (Principle 1, subprinciple 2 and Rule 56a) and violation to aim for stability of names, avoid useless creation of names (Principle 1, subprinciple 1 and 3) and that names should not be changed without sufficient reason (Principle 9 of the Code).

The genus *Borrelia*, initially described by Swellengrebel 1907, was divided by Adeolu and Gupta (Adeolu and Gupta, 2014) into two genera, one retaining the name *Borrelia* (comprising largely species associated with tick-borne relapsing fever illnesses), the other named *Borrelia* gen. nov. containing species of the *Borrelia burgdorferi* sensu lato species complex (which cause Lyme borreliosis). Subsequent work showed that the genus separation was based on

insufficient data and the drawn conclusions are only supported by a subset of *Borrelia* species (Margos et al., 2017; Margos et al., 2018; Estrada-Peña and Cabezas-Cruz, 2019; Margos et al., 2019). Following publication of the genus separation the names of eight out of 20 species were validated in the Validation List 163 (Oren and Garrity, 2015). In a later list (Oren and Garrity, 2018) three further species were re-named. As this will generate confusion amongst medical practitioners and health professionals, and it may seriously affect human health and welfare.

Risks to human health and patient safety

Lyme borreliosis (also called Lyme disease) is the most common arthropod-borne bacterial disease of humans in North America and Europe affecting an estimated 300,000 people each year in the USA, and, according to health insurance data, over 200,000 cases of Lyme borreliosis occur every year in Germany alone (Steere, 2001; Stanek and Strle, 2009; Muller et al., 2012; Radolf et al., 2012; Nelson et al., 2015; Schwartz et al., 2017; Sykes and Makiello, 2017).

Symptoms of Lyme borreliosis can vary widely among patients and may include characteristic skin lesions, arthritis, meningitis, radiculoneuritis, facial nerve paralysis, ocular involvement, and atrioventricular nodal block (Steere, 2001; Pinto, 2002; Stanek and Strle, 2003; Forrester and Mead, 2014; Hegerova and Olson, 2014; Kuchynka et al., 2015; Robinson et al., 2015). Notably, symptoms caused by some relapsing fever species, e.g. *B. miyamotoi*, may resemble that of Lyme borreliosis (Telford et al., 2015; Boden et al., 2016). Failure to treat this infection during the early stages can result in later severe clinical manifestations that may be more difficult to treat, such as Lyme arthritis and acrodermatitis chronica atrophicans. A missed or delayed diagnosis of Lyme carditis might even contribute to patient mortality (Steere, 2001; Stanek and Strle, 2003; Koene et al., 2012; Forrester and Mead, 2014; Shenthar et al., 2014; Yoon et al., 2015). Due to considerations of human health and welfare, we respectfully ask the Judicial Commission to reject *Borreliella* gen. nov. and all new combinations contained in it as

nomen periculosum, (as per Rule 56a of the International Code of Nomenclature of Prokaryotes) (Parker et al., 2015). Following this guidance, we describe safety concerns pertaining to changing the genus name of Lyme borreliosis-causing spirochetes:

1. The names “Lyme borreliosis” and “*Borrelia*” are thoroughly intertwined in medical literature. It is imperative that physicians and other care givers receive prompt and accurate information when diagnosing and treating patients. New information on treatment recommendations or diagnostic tests is frequently published. From discovery onward, all publications on Lyme borreliosis describe the causative bacteria as members of the genus *Borrelia*. Only the paper on renaming the genus (Adeolu and Gupta, 2014), and few others, even mention the word “*Borrelia*.”
2. Throughout the world, countless databases store diagnostic and treatment information. Search algorithms are usually based on keyword matches in order to retrieve the requested information. Thus, a search for *Borrelia* will likely fail to identify information that uses the name *Borrelia*, and vice versa. There is significant potential that such a failure could lead to diagnostic confusion and sub-optimal patient treatment, increasing the potential of poor outcomes for patients. Overcoming this problem would require replacement of every database and/or access program throughout the world, which is not a practical solution. The possible risk to human health far outweighs any benefit of the proposed bacterial species name change.
3. In some countries, payment for the delivery of diagnostic testing services and clinical care to patients is highly dependent upon the use of standardized, precise disease codes and procedural codes (e.g. ICD-10, CPT in the USA). Such coding in hospitals, clinics, health care systems and insurance companies is indeed based on the terminology “*Borrelia*.” Inconsistencies in coding and related descriptors in computer systems, along

with debates about whether *Borrelia burgdorferi* is the same causative agent as *Borrelia burgdorferi*, present genuine risks of confusion, denial of claims, and delay in proper insurance coverage. Consequently, access to diagnosis and treatment may be compromised, which could endanger the patient's health.

4. Government regulations vary around the world. Similarly, health insurance coverages and procedures vary extensively. A diagnostic test or treatment regimen with approved use for treating infections by *Borrelia burgdorferi* sensu lato may not automatically be accepted for *Borrelia burgdorferi*. In such cases, a patient may be denied treatment or misdiagnosed. Again, this potential threat to human health needs to be of primary concern.
5. Lyme borreliosis is a professional and public risk in many countries for persons using forested or grassy areas for work (eg. forestry) or recreation. Public health interventions including education materials rely heavily on the terminology *Borrelia* to properly inform the public and industry stakeholders about this pathogen, the risk of infection, and how to limit exposure. Specific diagnosis and treatment are often covered by professional insurance programs; debates about *Borrelia* as being the same as *Borrelia* has the potential to delay proper insurance coverage and, consequently, diagnosis and treatment. This endangers the patient's health and – by consequence – further employment.

Violation of Principle 1, subprinciple 1 and 3, and Principle 9 of the Code

Although the International Code of Nomenclature of Prokaryotes (ICNP) is concerned mainly with taxonomical nomenclature, it is difficult to completely separate this from other taxonomical disciplines such as classification and characterization. The preface of the latest

edition of the Code holds that “While the Code does not attempt to interfere with the process of classification it does lay down clear rules that stipulate that taxa must be distinguishable, that types must be properly designated and (where appropriate) authentic strains must be made available without restriction, and that data on which descriptions are based must be included. The Code provides the critical links between nomenclature, classification and characterization.....”, we would like to raise some critical issues regarding the separation of the genus *Borrelia* affecting its nomenclatural changes.

6. The genus *Borrelia* emend. Margos et al. 2018 currently comprises 42 named species (LPSN bacterio.net) including 21 species within the relapsing fever-associated group (RF), 20 species within the Lyme borreliosis-associated group (LB), and one species (*B. turcica*) within the novel reptile-associated group. However, there is a wide diversity of borreliae not represented by official named species (Mitani et al., 2004; Lin et al., 2005; Takano et al., 2011; Fedorova et al., 2014; Ivanova et al., 2014; Fingerle et al., 2016; Loh et al., 2017; Kumagai et al., 2018). Some of these novel *Borrelia* species phylogenetically cluster within previously characterized borreliae lineages such as *Candidatus Borrelia texasensis*, *Candidatus Borrelia kalaharica*, and *Borrelia* sp. from Tanzania in the argasid-transmitted RF clade, and *B. chilensis* in the *Ixodes*-transmitted LB clade (Mitani et al., 2004; Lin et al., 2005; Ivanova et al., 2014; Fingerle et al., 2016). However, more significant is the extensive diversity of *Borrelia* being described from metastriate ticks that form deeply branching unique monophyletic lineages within the genus. Such species include *Candidatus Borrelia tachyglossi* from echidnas (Loh et al., 2017), several novel species from Testudines (Takano et al., 2011), lizards (Panetta et al., 2017; Kaenkan et al., 2019; Supriyono et al., 2019), and snakes (Takano et al., 2010), and two putative species associated with *Haemaphysalis* spp. and Asian deer (Kumagai et al., 2018).

The proposal by Adeolu and Gupta (2014) to splitting the genus *Borrelia* into two, *Borrelia* (relapsing-fever group spirochaetes) and a novel genus *Borreliella* (Lyme borreliosis group spirochaetes) (Adeolu and Gupta, 2014) left out all of the metastriate-transmitted *Borrelia* species, the inclusion of which significantly alter our understanding of borreliae evolution.

7. The authors described conserved signature indels (CSIs) and conserved signature proteins (CSPs) that could distinguish between the LB *Borrelia* and the RF *Borrelia* groups. The description of the new genera indicated that only these genetic markers are able to distinguish the two genera while there is overlap in morphology (e.g. helical cells, 0.2-0.3 μm in width, 3-180 μm in length [the latter being a mistake as cells of both groups are usually 10-30 μm in length]), phenotypic traits (e.g. motility via periplasmic flagella, microaerophily, vector-transmission) and genomic GC content (26-32 %) of the two groups. As we have previously pointed out, it is uncontested that differences in CSI and CSP exist between the clade of LB and RF species (Margos et al., 2018), there are similarities and overlaps in traits that need to be taken into consideration when studying taxonomy (Table). Apart from a common morphology that is shared by spirochetal bacteria (with some variations within groups, e.g. number of flagella, number and regularity of spirals), a similar genome structure, similar GC content, a further common property of species within the genus *Borrelia* is that they are with one exception maintained in natural transmission cycles by ticks as vector. Thus, it is our view that the renaming is based on selected genomic characters, i.e. on CSIs and CSPs in only two of the clades contributing to the genus *Borrelia*. In a third clade of species (e.g. *B. turcica*, *Candidatus B. tachyglossi* which have been subsumed under RF species by Gupta, 2019) 17-20% of these characters do not follow the predicted pattern of having RF specific CSIs but have a signature of LB CSIs. In our opinion this disregards principle 1 subprinciple 3 of the Code ('Avoid the useless

creation of names’) and principle 9 (The name of a taxon should not be changed without sufficient reason....) and is in conflict with the statement in the preface (...it [the Code] does lay down clear rules that stipulate that taxa must be distinguishable...).

8. Following division of the genus *Borrelia* into two separate genera, 14 species out of 20 species were renamed in the new genus *Borreliella* (Adeolu and Gupta, 2014) and 11 validated in IJSEM (Oren and Garrity, 2015; Oren and Garrity, 2018). We would like to highlight that in 2018 and 2019, two independent studies evaluated a justification of the genus separation (Margos et al., 2018; Estrada-Peña and Cabezas-Cruz, 2019). The first study sequenced the genomes of species “intermittent” between the relapsing fever clade and the *B. burgdorferi* s.l. clade, a reptile-associated and a newly described echidna-associated species (Gofton et al., 2018; Margos et al., 2018). Data based on the percentage of conserved proteins (POCP) (Qin et al., 2014) and on clustering of CSIs suggested that all groups should remain within a single genus (Margos et al., 2018). Independently, using a phyloproteomics approach the second study concluded that the separation of relapsing fever and Lyme borreliosis group spirochetes was not supported by their data (Estrada-Peña and Cabezas-Cruz, 2019). A recent review that included a phylogenetic analysis of near full length 16S rRNA sequences of all reported *Borrelia* species showed that many strains and species need to be evaluated before judgement is justified on the genus as a whole (Margos et al., 2019).

Given the situation outline above, the proposed changes in *Borrelia* taxonomy, i.e. the creation of two different genera is a violation of principle 1, subprinciples 1 and 3 of the Code as the proposed changes are premature, i.e. based on insufficient data, which does not support stability of names (violation of subprinciple 1) and uselessly creates new names (subprinciple 3). The latest publication by Gupta (Gupta, 2019) on *Borrelia* taxonomy reiterates results of earlier studies and thus violates principle 9 of the Code which states that “The name of a taxon should

not be changed without sufficient reason based either on further taxonomic studies or on the necessity of giving up a nomenclature that is contrary to the Rules of this Code.”

The genus *Borrelia* is currently validated in its original form (Oren and Garrity, 2019) and other analyses such as proteomics, analyses of phenotypic and ecological data are consistent with this view (Margos et al., 2019). For this and the reasons outlined above we would like to ask the Judicial Commission to support the rejection of the name *Borreliella* gen. nov. and all combinations therein.

Table *Borrelia* – key features of clades

Clade	<i>Borrelia burgdorferi</i> sensu lato	Relapsing fever group of spirochaetes	Reptile- and echidna-associated spirochaetes
Morphology*	motile spirochaetal bacteria, helically shaped with tapered ends; diderm membrane architecture (outer surface membrane, periplasmic space, peptidoglycan-cytoplasmic membrane); periplasmic flagellae (n=4-14); 0.2 – 0.3 µm diameter 10-30 µm in length	motile spirochaetal bacteria, helically shaped with tapered ends; diderm membrane architecture (outer surface membrane, periplasmic space, peptidoglycan-cytoplasmic membrane); periplasmic flagellae (n=8-20); 0.2-0.5 µm diameter 10-40 µm in length	motile spirochaetal bacteria, helically shaped with tapered ends; periplasmic flagellae (n=10); 0.2 – 0.3 µm diameter 10-25 µm in length
Genomic features*	Fragmented genome, Linear chromosome, plasmids (5-70 kb) Size 1.5 Mb GC content 28%; common ancestry of plasmids cp26 (all LB) and lpB (<i>B. miyamotoi</i>)	Fragmented genome, linear chromosome, plasmids (5-165 kb), Size 1.5 Mb GC content 27-30%; common ancestry of plasmids cp26 (all LB) and lpB (<i>B. miyamotoi</i>)	Fragmented genome, linear chromosome, Plasmids (30-130) Size 1.5 Mb GC content 30%
Vector species	hard tick genus <i>Ixodes</i>	hard-ticks of genera <i>Ixodes</i> , <i>Rhipicephalus</i> , <i>Amblyomma</i> , <i>Haemaphysalis</i>	hard-tick genera <i>Hyalomma</i> , <i>Amblyomma</i> , <i>Ixodes</i> , <i>Bothriocroton</i>

		Soft tick genera <i>Ornithodoros</i> , <i>Argas</i> ; body louse <i>Pediculus humanus</i> [#] ;	
Pathogenicity profile*	Commonly tissue pathogens, transient blood phase except in <i>B. mayonii</i> (blood densities up to 10 ⁵ –10 ⁶ cells / ml).	Commonly found in blood before/during febrile periods but colonize also tissue. For many unknown. <i>B. duttonii</i> is well known to cross the placenta causing peri-natal mortality; <i>B. miyamotoi</i> infection may resemble Lyme (neuro)borreliosis.	Unknown
transovarial transmission	rare, shown for <i>B. afzelii</i> [§]	common	unknown

*information is available only for a subset of species, not for all species.

[#]the louse may not be considered a proper vector because transmission occurs when the louse is crushed and gut content is smeared into the skin

[§] (van Duijvendijk et al., 2016)

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