INTERNATIONAL JOURNAL OF SYSTEMATIC AND EVOLUTIONARY MICROBIOLOGY

REQUESTS FOR AN OPINION

MICROBIOLOGY

Margos et al., Int. J. Syst. Evol. Microbiol. 2020;70:3577–3581 DOI 10.1099/ijsem.0.004149

Rejection of the name *Borreliella* and all proposed species comb. nov. placed therein

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Abstract

Rejection (nomen rejiciendum) of the name Borreliella 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, to 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 International Code of Nomenclature of Prokaryotes).

INTRODUCTION

The genus *Borrelia*, initially described by Swellengrebel 1907, was divided by Adeolu and Gupta [1] into two genera, one retaining the name *Borrelia* (comprising largely species associated with tick-borne relapsing fever illnesses), the other named *Borreliella* gen. nov. containing species of the *Borrelia burgdorferi* sensu lato species complex (which cause Lyme borreliosis). Subsequent work has shown that the genus separation was based on insufficient data and the drawn conclusions are only supported by a subset of species of the genus *Borrelia* [2–5]. Following publication of the genus separation the names of eight out of 20 species were validated in Validation List 163 [6]. In a later list [7] three further species were re-named. As this will generate confusion amongst medical practitioners and health professionals, 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 [8–14].

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 [10, 15–20]. Notably, symptoms caused by some relapsing fever species, e.g. *B. miyamotoi*, may resemble that of Lyme borreliosis [21, 22]. 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

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Keywords: Borrelia; Lyme disease; nomenclature.

Abbreviations: CSI, conserved signature indel; CSP, conserved signature protein; LB, Lyme borreliosis; RF, relapsing fever. A supplementary figure is available with the online version of this article.

chronica atrophicans. A missed or delayed diagnosis of Lyme carditis might even contribute to patient mortality [10, 15, 17, 23–25]. Due to considerations of human health and welfare, we respectfully ask the Judicial Commission to reject *Borreliella* and all new combinations contained in it as *nomina periculosa* (as per Rule 56a of the International Code of Nomenclature of Prokaryotes) [26]. Following this guidance, we described safety concerns pertaining to changing the genus name of Lyme borreliosis-causing spirochetes [27]:

- 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 [1], and few others, even mention the word 'Borreliella' (22 times used as author keyword since 2012–2019 compared with 1255 times for Borrelia as per scopus search 20/12/2019).
- 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 *Borreliella* will be likely to 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 Borreliella 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 *Borreliella burgdorferi*. In such cases, a patient may be denied treatment or misdiagnosed. Again, this risk to human health needs to be of primary concern.

5. Lyme borreliosis is an occupational and public risk in many countries for persons using forested or grassy areas for work (e.g. 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 *Borreliella* as being the same as *Borrelia* have the potential to delay proper insurance coverage and, consequently, diagnosis and treatment. This endangers the patient's health and – in consequence – further employment.

Violation of Principle 1, subprinciples 1 and 3, and Principle 9 of the International Code of Nomenclature of Prokaryotes

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 [3] currently comprises 43 named species (LPSN bacterio.net) including 21 species within the relapsing fever-associated group (RF), 21 species within the Lyme borreliosis-associated group (LB), and one species (Borrelia turcica) within the novel reptile-associated group. However, there is a wide diversity of borreliae not represented by official named species [28-35]. Some of these novel species of the genus Borrelia 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 [28, 29, 32, 33]. However, more significant is the extensive diversity of members of the genus Borrelia being described from metastriate ticks that form deeply branching unique monophyletic lineages within the genus. Such species include Candidatus Borrelia tachyglossi from echidnas [34], several novel species from Testudines [30], lizards [36-38], and snakes [39], and two putative species associated with Haemaphysalis spp. and Asian deer [35] (Fig S1 in online version).

The proposal by Adeolu and Gupta [1] to split the genus *Borrelia* into two, *Borrelia* (relapsing-fever group spirochetes) and a novel genus *Borreliella* [Lyme borreliosis (LB) group spirochetes] [1] left out all of the metastriate-transmitted

 Table 1. Borrelia – key features of clades (Table from https://doi.org/10.1016/j.ttbdis.2019.101335)

| Clade | Borrelia burgdorferi sensu lato | Relapsing fever group of spirochetes | Reptile- and echidna-associated spirochetes |
|---------------------------|--|---|--|
| Morphology* | Motile spirochaetal bacteria, helically shaped with tapered ends; diderm membrane architecture (outer surface membrane, periplasmic space, peptidoglycan-cytoplasmic membrane); periplasmic flagella (<i>n</i> =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 flagella (n=8–20); 0.2–0.5 µm diameter 10–40 µm in length | Motile spirochaetal bacteria, helically shaped with tapered ends; periplasmic flagella (<i>n</i> =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 DNA G+C 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 DNA G+C content 27–30 %; common ancestry of plasmids cp26 (all LB) and lpB (<i>B. miyamotoi</i>) | Fragmented genome, linear chromosome, plasmids (30-130 kb) Size 1.5 Mb DNA G+C content 30% |
| Vector species | Hard ticks of genus <i>Ixodes</i> | Hard ticks of genera Ixodes, Rhipicephalus, Amblyomma, Haemaphysalis Soft ticks of genera Ornithodoros, Argas; Body louse Pediculus humanus;† | Hard ticks of genera <i>Hyalomma</i> , Amblyomma, Ixodes, Bothriocroton |
| Pathogenicity profile* | Commonly tissue pathogens, transient blood phase except in <i>B. mayonii</i> (blood densities up to 10^5 – 10^6 cells ml $^{-1}$). | 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 B. afzelii§ | Common | Unknown |

^{*}Information is available only for a subset of species, not for all species.

8[45].

species of the genus 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 be used to 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 DNA G+C content (26-32 mol%) of the two groups. As we have previously pointed out, it is uncontested that differences in CSI and CSP exist between the clades of LB and RF species [3], however there are similarities and overlaps in traits that need to be taken into consideration when studying taxonomy (Table 1). 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 DNA G+C 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 vectors. 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* and *Candidatus* B. tachyglossi which have been subsumed under RF species by [40]), 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 out of 20 species were renamed in the new genus *Borreliella* [1] and 11 validated in IJSEM [6, 7]. We would like to highlight that in 2018 and 2019, two independent studies evaluated a justification of the genus separation [2, 3]. The first study sequenced the genomes of species 'intermittent' between the RF clade and the LB clade, a reptile-associated and a newly described echidna-associated species [3, 41].

[†]The louse may not be considered a proper vector because transmission occurs when the louse is crushed and gut contents are smeared into the skin.

Data based on the percentage of conserved proteins (POCP) [42] and on clustering of CSIs indicated that all groups should remain within a single genus [3]. Independently, using a phyloproteomics approach the second study concluded that the separation of RF and LB group spirochetes was not supported by their data [2]. A recent review that included a phylogenetic analysis of near full length 16S rRNA sequences of all reported species of the genus *Borrelia* revealed that many strains and species need to be evaluated before judgment is justified on the genus as a whole [5] (see Fig. S1, available in the online version of this article).

Given the situation outline above, the proposed changes in taxonomy of the genus *Borrelia*, 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 [40] on taxonomy of the genus *Borrelia* 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.'

Moreover, there is also confusion amongst the scientific community as a result of splitting the genus *Borrelia* into two. Most notably, researchers have experienced frustration during the submission of sequence data to online databases, such as the NCBI sequence database GenBank [43], whereby sequences have been incorrectly renamed post-submission as *Borreliella*. For example, despite the original submission as *Candidatus* Borrelia tachyglossi and supporting evidence that it does not cluster within the LB species clade, it was renamed as *Candidatus* Borreliella tachyglossi. The name has since been reverted to the genus *Borrelia*, however, the genus *Borreliella* remains as a synonym within the sequence metadata (e.g. GenBank Accession CP025785 and KY586964) [34, 41].

The genus *Borrelia* is currently validated in its original form [44] and other analyses such as proteomics, analyses of phenotypic and ecological data are consistent with this view [5]. For this and the reasons outlined above we would like to ask the Judicial Commission to support the rejection of the name *Borreliella* and all combinations therein.

Funding information

The National Reference Center for Borrelia was supported by the Robert Koch-Institute, Berlin, Germany.

Acknowledgements

At the business meeting of ESGBOR, Amsterdam 2019 it was discussed that the genus 'Borrelia' is the preferred terminology.

Author contributions

G.M., V.F., B.S., A.G., C.O., A.E-P., S.C., I.S., G.W. conceptualization S.C-R., I.R. resources All authors reviewed and edited the ms

Conflicts of interes

The author(s) declare that there are no conflicts of interest.

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