Emerging borreliae – expanding beyond Lyme borreliosis

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ABSTRACT
Lyme borreliosis (or Lyme disease) has become a virtual household term to the exclusion of other forgotten, emerging or re-emerging borreliae. We review current knowledge regarding these other borreliae, exploring their ecology, epidemiology and pathological potential, for example, for the newly described B. mayonii. These bacteria range from tick-borne, relapsing fever-inducing strains detected in some soft ticks, such as B. mvumii, to those from bat ticks resembling B. turicatae. Some of these emerging pathogens remain unnamed, such as the borrelial strains found in South African penguins and some African cattle ticks. Others, such as B. microti and unnamed Iranian strains, have not been recognised through a lack of discriminatory diagnostic methods. Technical improvements in phylogenetic methods have allowed the differentiation of B. merionesi from other borrelial species that co-circulate in the same region. Furthermore, we discuss members that challenge the existing dogma that Lyme disease-inducing strains are transmitted by hard ticks, whilst the relapsing fever-inducing spirochaetes are transmitted by soft ticks. Controversially, the genus has now been split with Lyme disease-associated members being transferred to Borreliella, whilst the relapsing fever species retain the Borrelia genus name. It took some 60 years for the correlation with clinical presentations now known as Lyme borreliosis to be attributed to their spirochaetal cause. Many of the borreliae discussed here are currently considered exotic curiosities, whilst others, such as B. miyamotoi, are emerging as significant causes of morbidity. To elucidate their role as potential pathogenic agents, we first need to recognise their presence through suitable diagnostic approaches.

Key words: Emerging Borrelia; tick-borne; Lyme; Relapsing Fever; REP; Borreliosis.
1. Understanding borrelial taxonomy

When one mentions the genus *Borrelia*, it conjures up the thought of Lyme borreliosis (or Lyme disease); however, the genus contains a heterogeneous range of borreliae with an increasingly recognised diversity. The type species for the genus is *Borrelia anserina*, a borrelial spirochaete transmitted by soft ticks of the genus *Argas*, including *A. persicus*. Amedee Borrel noted that this organism, *B. anserina*, showed distinct differences when compared with the other known spirochaete described at the time, *Treponema pallidum*. Although his interpretation of its morphology was flawed in that he described it with peritrichous flagellae, his first description of this species was subsequently honoured with his name [1]. Today, this species is only rarely reported [2-4], but can have a devastating impact upon poultry, its preferred host. Improvements in poultry housing have resulted in the demise of its tick vector and, consequently, the infection; however, this pathogen remains problematic in sub-Saharan Africa and other developing countries [4].

Following the original description of this genus, *Borrelia*, description of relapsing fever-inducing borreliae associated with differing vectors ensued. Historically, the borreliae were classified by the “one vector one species” concept that additionally incorporated geographical location and virulence in animal models [5]. These spirochaetes were collectively considered under the rather arbitrary groupings of Old World and New World borreliae. The subsequent description of the Lyme-associated species enabled comparison of these deeply divergent clades within the genus. Phylogenetic differences appeared to relate to ecological divides with the relapsing fever species being vectored by soft ticks (with the exception of the human louse-borne *Borrelia recurrentis*), whilst the Lyme disease-associated species were transmitted by hard-bodied ixodid tick species. The recognition of many distinct entities causing Lyme borreliosis and closely related spirochaetes with apparently less pathogenic potential has resulted in this group being known as the *Borrelia burgdorferi* sensu lato complex. This “dogma” held for many years, but is now becoming blurred with the discovery of relapsing fever group spirochaetes that are also transmitted by ixodid ticks (see section below).

Many scientists who are searching for ATCC type strains or depositing GenBank sequences may stumble across a presumptive novel genus aligned within the borreliae, classified as genus *Borreliella* gen. nov. [6]. This proposed terminology arises from the analysis of concatenated sequence data for 25 housekeeping proteins derived from the genomic sequences of 38 *Borrelia* strains representing 18 species. The deeply rooted divergence demonstrated between the relapsing fever-inducing and Lyme disease groups of borreliae, corroborating previous findings, resulted in the newly suggested name of *Borreliella* to be applied to members of the latter group that were described after those of the former group [6]. Many researchers in the field who see this only serving to add confusion to the already complicated taxonomy of this spirochaetal group have largely not welcomed this proposed new genus name. Although currently hotly debated, judgement by appropriate taxonomic committees will be necessary to resolve this debate.

2. New players and emerging concepts in the Lyme borreliosis arena

The Lyme associated members have expanded over recent years, largely through the application of highly discriminatory molecular typing that can discern distinct groups within this spirochaetal complex (see Table 1 for a list of current species). Although
the pathogenic potential of many of these variants remains to be established, recognition is an essential first step towards unravelling their ecological role(s) and pathogenic capability. Within this category are borreliae, including *B. americana*, *B. bavariensis*, *B. bissettiae*, *B. californiensis*, *B. finlandensis*, *B. kurtenbachii*, *B. mayonii*, *B. sinica*, *B. tanukii*, *B. turdi* and *B. yangtzensis*, which share their vector with known pathogenic species. This raises the possibility of mixed infections and thus complicates assessment of pathogenic potential of these newly recognised species. Furthermore, some show geographical divide into “Old World” or “New World” species; however, others, such as *B. bissettiae* and *B. carolinensis*, have global distribution [7].

The ecological cycle for Lyme borreliosis has been extensively studied over the years, with the role of rodents as essential vertebrate reservoirs being established as being of paramount importance. Indeed, exceptions to known ecological associations have provided clues as to undifferentiated species misclassified amongst close genotypic relatives such as the inclusion of *B. bavariensis* as a rodent-adapted variant of the avian-adapted *B. garinii* species [8]. Even amongst *B. bavariensis* alone, strain diversity is becoming increasingly recognised [9]. It is undoubtedly true that rodents have a vital part to play in the ecology of Lyme borreliosis, but this has given an unconscious bias away from the role of other vertebrate species and their significance in maintaining ecological cycles for Lyme borreliae. Similarly, it is believed that tick species with diverse hosts will maintain greater diversity amongst the borreliae that they carry; however, this proposal is challenged by findings of greater diversity amongst *B. garinii* detected in the sea-bird feeding tick *Ixodes uriae* when compared with the diversity of *B. garinii* detected within *I. ricinus* ticks [10].

The recent description of *B. mayonii* has drawn attention as a potentially more virulent member of the *B. burgdorferi* sensu lato complex, also transmitted by *I. scapularis* [11]. Current evidence suggests that this organism produces higher numbers of spirochaetes in the blood than its *B. burgdorferi* sensu stricto counterpart. Whether this impacts upon other clinical consequences remains to be elucidated. Intriguingly, when virulence is compared between or among members of the same species, but derived from either European or American locations, differences have been reported in clinical presentation as well as in their ability to provoke cytokine and chemokine cascades associated with induction of both innate and Th1 immune reactivity [12]. It is probable that sub-species “pathotypes” might account for differences in immunostimulatory potential between isolates from both sides of the Atlantic.

3. Emerging relapsing fever borreliae

As evidenced for the Lyme borreliae, the impact of discriminatory molecular approaches has resulted in change. In some cases there has been rediscovery of forgotten species, such as *B. merionesi* [13, 14], whilst new species have been described, including *B. miyamotoi*, and proposed Candidatus species *B. johnsonii*, *B. lonestari*, *B. mvumii* and *B. texansensis* (see Table 2 for a list of names). Geographic areas, such as Iran, have reported clinical cases of relapsing fever associated with spirochaetes that align most closely with species present in East Africa [15]. Whether this is a unique description or rediscovery of *B. baltazardi* or *B. latyschewii* remains unresolved given the absence of publicly available sequence data (in GenBank) for these spirochaetes. Similarly, another relapsing fever-inducing spirochaete has been reported in both human blood and ticks of the *Ornithodoros moubata* complex in
Tanzania [16, 17]. Surprisingly, this strain, Candidatus B. mvumi, showed greater homology to B. hermsii rather than the relapsing fever-inducing species known to be endemic in East Africa [18]. These findings are echoed by the description of a case of relapsing fever presumably acquired by a traveller returning from the Kalahari Desert, Candidatus B. kalaharica, which similarly resembled “New World” species [19].

Sporadic reports have been published, describing other relapsing fever-like organisms, but their pathogenic significance remains unclear. Frequently, bats colonise buildings, thus bringing both bats and their ticks into close proximity to humans. A study of the soft bat tick, Argas vespertilionis (also known as Carios vespertilionis), in France revealed the presence of a relapsing fever-inducing Borrelia species (CPB1) akin to that linked to a fatal infection in a bat in the UK [20, 21].

Sporadic reports of a relapsing fever Borrelia closely related to B. turicatae have been published, but a comprehensive phylogenetic comparison with existing species has not been conducted [22-24]. The name Candidatus Borrelia johnsonii has been proposed for this Carios kelleyi spirochaete [24].

The presence of relapsing fever-inducing infections in livestock and wildlife have been reemphasised in recent publications [4, 25-27]. Indeed, infections by B. theileri can be considered as being rediscovered. This infection has veterinary significance and appears to exist in regions where diagnostic ability is limited; hence, its impact on productivity is largely unexplored. Notably, this species, despite belonging to the relapsing fever borreliae, is transmitted by hard ticks, such as Rhipicephalus (Boophilus). Phylogenetically, B. theileri clusters closely with another hard tick-transmitted, relapsing fever-inducing species described in the USA, B. lonestari, which is transmitted by Amblyomma americanum and other species of predominantly hard ticks [28]. Amblyomma americanum is particularly aggressive and has recently been shown to carry other potential pathogens making clinical attribution to B. lonestari complicated [29]. Though not yet cultivated in axenic medium, B. lonestari has been associated with human skin lesions following tick bite. Furthermore, it is believed to interfere with serological test results for Lyme borreliosis. Recently, a B. lonestari-like organism has been reported in Haemaphysalis ticks and Sika deer (Cervus nippon yesoensis) in Japan [30], suggesting that this species has a much more global distribution than previously appreciated. This observation is further corroborated by the finding of a closely related sub-group of relapsing fever-inducing Borrelia species residing in Haemaphysalis punctata and Rhipicephalus sanguineus ticks collected from Portugal [31]. To challenge existing dogma even further, this species has additionally been detected in Argas spp., thus occurring in both hard and soft tick species, with its presence being detected in the seabird tick Carios capensis [32].

In wildlife, there have been reports of a relapsing fever-inducing species of Borrelia infecting penguins at a rehabilitation centre in South Africa. [33]. This spirochaete resembled a novel relapsing fever-inducing species identified within Carios sawaii ticks feeding on seabirds [34]. Furthermore, there are reports of a relapsing fever-inducing spirochaete with greatest homology with B. turicatae reported from Dermacentor variabilis feeding upon coyote in Texas, USA. This has tentatively been designated Candidatus B. texensis [35], and was followed by reports of B. turicatae in dogs in Texas [36]. The recognition that dogs are susceptible to relapsing fever-inducing spirochaetes has been followed by other members of this group, such as B. hermsii and B. persica, which cause canine infections [37, 38].
Unresolved dilemmas were raised by the discovery of *B. miyamotoi*, a relapsing fever-inducing spirochaete that is vectored by hard tick species (*I. scapularis*, *I. persulcatus* and *I. ricinus*). *Borrelia miyamotoi* is another member affiliated with the relapsing “fever group of species” and, like *B. lonestari* above, is also transmitted by hard ticks. This spirochaete was first described in Japan, where it was isolated from *I. persulcatus* ticks collected in Hokkaido, but this report was soon followed by descriptions from the USA and Russia, and later throughout Europe [39]. Initially treated as an anomaly, this species has recently drawn global attention with recognition of its ability to cause human infection. Clinical features and diagnostics can overlap with Lyme borreliosis and are likely to have obscured its recognition as a species that is pathogenic in humans. Although clustering amongst the relapsing fever group, and, indeed, possessing variable small and large proteins [40], the clinical presentation is not characteristic of classical relapsing fever [41, 42]. Now that its infectious potential has been established and increasing reports are being accrued from Eurasia, Europe and the USA [42-44], it is apparent that three genotypes exist within this species showing geographical separation within US, Europe and the Russia-Far East [45].

Subsequently, further *Borrelia* that appear to represent the relapsing fever-inducing group, but have been found in hard tick species are being disclosed. Japanese studies have revealed a relapsing “fever-like” spirochaete (AGRF) present in *Amblyomma* *geoemydae* ticks [46]. A relapsing “fever-like” spirochaete has been reported from blood films collected from penguins at a rehabilitation unit in South Africa [33]. Interestingly, Lyme disease-associated borreliae have also been described to infect penguins, presumably through exposure to *I. uriae* [47].

4. The non-conformist third borrelial cluster

Another “orphan” *Borrelia* was described in *Hyalomma aegyptium* ticks removed from tortoises in Turkey [48, 49]. Now named *B. turicata* (also known as REP or tAG; see table 3), these spirochaetes have a natural ecology involving reptiles and their ticks [50, 51]. Phylogenetic analysis of these *Borrelia* taxa has revealed that they are deeply divergent from both the Lyme disease-associated clade and those causing relapsing fever, justifying their inclusion as a separate cluster within the over-arching genus of *Borrelia* [50, 51]. Intriguingly, these presumed reptile-associated species have subsequently been detected in *Amblyomma maculatum* collected in the Gulf Coast [52]. Similarly, related *Borrelia* have been detected in *Amblyomma varanense* collected from pythons in Thailand [53]. These findings suggest a global dispersion of these borreliae.

Closely related to these stains, but potentially distinct are newly described *Borrelia* species identified in *Ixodes holocyclus* (Australian tick paralysis species) removed from the echidna (Tachyglossidae) [54, 55]. The presence of Australian borreliae has long been predicted, and this tick species is known to feed upon multiple vertebrate species, thus may account for serological exposure to borreliae in humans in Australia. Other reports have described a novel *Borrelia* species present in ticks collected from cattle in Ethiopia that fails to cluster with either Lyme disease-associated or relapsing fever-inducing borreliae [56]. These observations underscore our incomplete understanding of this genus and its diverse members.

5. Future perspectives
It is apparent in this brief review that we have a multitude of knowledge gaps and unanswered questions. For those Lyme borreliae established as pathogens, we have yet to explore the reasons for differential virulence and tissue tropisms. Exploration of the cross-talk between spirochaete and host responses is an essential pre-requisite to decipher pathological mechanisms. Indeed, application of high-resolution genetic typing tools, in conjunction with assessment of the host inflammasome, might yield greater insights towards this goal, but much research remains to be done.

With the advent of more whole genome studies, it is probable that we will gain a deeper understanding of borrelial diversity. The impact of molecular techniques has enabled us to explore the diversity of borrelial species using targeted approaches. However, technological improvements enabling multiplex analysis or even whole genome studies are resulting in us stumbling across more unexpected findings that challenge existing dogma. From such studies, it is anticipated that improved diagnostics will emerge. The need for improved molecular diagnostic approaches is becoming increasingly apparent, not only to embrace co-infections with other microbes, but also to address potential co-infection with other borrelial species.

6. Concluding remarks

Advances in molecular diagnostics have enabled us to start to explore the complexity within the borrelial genus. We are still firmly in the discovery phase, but molecular data sets are providing us with some insights into the intriguingly divergent host-microbial interfaces utilised by these enigmatic microbes. Exploration of host-microbial interactions of the both natural and accidental host species infections is likely to elucidate the pathological mechanisms employed and differences in immune response provoked by divergent strains and species. What is becoming increasingly apparent is that we need to reconsider our out-dated and rather simplistic model for these organisms, whereby the members of the Lyme disease group are transmitted by hard ticks, whilst the relapsing fever-inducing group are transmitted by soft ticks (with the exception of lice, in some cases).

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Table 1: Names of *B. burgdorferi* sensu lato complex.

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<th>Year</th>
<th>Reference</th>
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<td>1994</td>
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<td><em>B. americana</em></td>
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<td>[58]</td>
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<td><em>Candidatus</em> B. <em>andersonii</em></td>
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<td>[59]</td>
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<td>2013</td>
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<td><em>B. bissettiae</em></td>
<td>2016</td>
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<td><em>B. burgdorferi</em> sensu stricto</td>
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<td><em>B. carolinensis</em></td>
<td>2011</td>
<td>[63]</td>
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<td><em>B. chilensis</em></td>
<td>2014</td>
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<td><em>B. yangtzensis</em></td>
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Table 2: List of Relapsing Fever group borreliae.

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<td>[78]</td>
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<td>Candidatus B. johnsonii</td>
<td>2009</td>
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<tr>
<td>Candidatus B. kalaharica</td>
<td>2016</td>
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<td>B. latyschewii</td>
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<td>Candidatus B. lonstari</td>
<td>1996</td>
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<td>B. mazzottii</td>
<td>1956</td>
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<td>[90]</td>
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<td>B. merionesi</td>
<td>1947/8</td>
<td>Confirmed</td>
<td>[91]</td>
</tr>
<tr>
<td>B. microti</td>
<td>1947</td>
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<td>[92]</td>
</tr>
<tr>
<td>B. miyamotoi</td>
<td>1995</td>
<td>Confirmed</td>
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</tr>
<tr>
<td>Candidatus B. mvumii</td>
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<tr>
<td>B. parkeri</td>
<td>1942</td>
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<td>B. persica</td>
<td>1913</td>
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<td>[94]</td>
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<td>B. recurrentis</td>
<td>1874</td>
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<td>[95]</td>
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<tr>
<td>Candidatus B. texassensis</td>
<td>2005</td>
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<tr>
<td>B. theileri</td>
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<td>B. tillae</td>
<td>1961</td>
<td>Confirmed</td>
<td>[97]</td>
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<td>B. turicatae</td>
<td>1933</td>
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<tr>
<td>B. venezulensis</td>
<td>1921</td>
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Table 3: List of non-conformist borreliae

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<thead>
<tr>
<th>Name</th>
<th>Year</th>
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<tr>
<td><em>B. turica</em></td>
<td>2004</td>
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<tr>
<td><em>Candidatus B. queenslandica</em></td>
<td>1962</td>
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