VIRAS response to NICE request for comments

The NICE Draft Scope includes:
"4) The inclusion of the following strains of Lyme Borreliosis for consideration as part of our review of the evidence:
B. burgdorferi (and the subtype B. burgdorferi sensu stricto), B. garinii, B. afzelii"

Borrelia Species causing Lyme borreliosis and Travel Risks

Key Points

- Since the discovery of *borrelia burgdorferi* in 1982, more species and strains have been discovered and implicated in Lyme borreliosis (LB)
- As recently as 2016, the CDC and Mayo Clinic have announced a new LB species
- As recently as 2016 Rudenko *et al* (14) provide evidence of the involvement of *B. bissettii* in human Lyme borreliosis
- Regions endemic for LB species have expanded and are expected to continue to do so
- A high number of UK residents travel abroad with increased risk of exposure to a greater range of LB species and strains

The species of borrelia specific for 'Lyme Disease' were *b. burgdorferi s.s.*, *b. garinii* and *b. afzelii*. This artificial restriction has long been discarded by scientists and physicians to recognise additional borrelia species responsible for 'Lyme Borreliosis' (LB).

All authorities recognise LB as a growing threat. The World Health Organization Europe report on Lyme Borreliosis and Global Warming states (1): "Since the 1980s, tick vectors have increased in density and spread into higher latitudes and altitudes in Europe. It can be concluded that future climate change in Europe will facilitate a spread of LB into higher latitudes and altitudes, and contribute to increased disease occurrence in endemic areas." To meet this challenge, the Guidelines must recognise that non-endemic species could spread to the UK and accept the possibility of further unknown species and strains yet to be discovered.

In Scientific American's guest blog, *Lyme Time Is upon Us Again.* Pfiefer (2016)(2) remarks on *Ixodes ricinus*, (castor bean tick) which transmits LB in Europe: "In Europe, disease-ridden castor bean ticks, a relative of those in the U.S., are on the move too, spreading 300 miles north in Sweden and Norway to latitudes that were considered too cold only a generation ago. Prolific and resilient, they are even scaling mountains, climbing 1,300 feet up the Dinaric Alps of Bosnia and Herzegovina and moving to new heights in the Czech Republic and Scotland."

LB species causing disease in Europe include: *burgdorferi, afzelii, garinii, spielmanii, lusitaniae, valaisiana, bisettii* (Heyman *et al*. 2010)(3). Rizzoli *et al* state in Eurosurviellance (4): "LB is likely to become an increasingly relevant health risk in the near future due to complex interactions between diverse environmental and socio-economic factors, which will affect various aspects of disease ecology and epidemiology".

Risk to UK Residents Travelling Abroad

Worldwide species of Lyme borreliosis spirochaetes pose a threat to UK residents travelling abroad. The CDC (2015)(5) state that LB in Europe is: "endemic from southern Scandinavia into the northern Mediterranean countries of Italy, Spain, and Greece and eastward from the British Isles into central Russia."

According to the UK Government, British nationals make millions of visits abroad each year. This increases the risk of exposure to Lyme borreliosis and a greater diversity of LB species and strains.

Destination	Number of visits	LB incidence per 100k pop.
France	17 million	44
Germany	2 million	261
Netherlands	1.8 million	149
Austria	774,000	300
Switzerland	710,000	30
Sweden (Southern)	664,000	464
Czech Republic	300,000	38
Slovenia	100,000	155

UK reported incidence of LB per 100k pop:	
Scotland	5.9
England and Wales	1.73

(Source for travel abroad: https://www.gov.uk/foreign-travel-advice/france [change country name for other destinations in lowercase]) (Sources for incidence figures: see below)

According to the Office for National Statistics (6) 62% of travel abroad by UK residents is for a holiday and 11% for visits to friends and relatives and might therefore be expected to be of at least several days. Therefore each year there are millions of visits by British nationals to other European countries where LB incidence ranges from 17 to 268 times the 'official' rate in England and Wales. Notwithstanding UK incidence figures which appear to be absurdly low, the high numbers travelling abroad are subject to a significant risk of exposure to diverse species and strains of borrelia.

Pfiefer (2016)(7) observes: "In the Netherlands, rates of people diagnosed with the telltale Lyme rash ranged up to 514 per 100,000 in 2014. In areas of Germany and Sweden, studies of patient records found Lyme rates of 261 to 464 per 100,000. In Europe, the highest national rate—315 per 100,000 in 2009 – has been reported in Slovenia, one of few countries to aggressively track cases."

Travel to the USA

UK residents make over 3 million visits to the USA each year (6). The CDC (2013)(8) state: "Preliminary estimates released by the Centres for Disease Control and Prevention indicate that the number of Americans diagnosed with Lyme disease each year is around 300,000.

‘ “We know that routine surveillance only gives us part of the picture, and that the true number of illnesses is much greater,” said Paul Mead, M.D., M.P.H, chief of epidemiology and surveillance for CDC’s Lyme disease program. “This new preliminary estimate confirms that Lyme disease is a tremendous public health problem in the United States, and clearly highlights the urgent need for prevention.” ’

Kiersten *et al* (2015)(9) state, “Over time, the number of counties in the northeastern states identified as having high incidence of Lyme disease increased >320%: from 43 (1993–1997) to 90 (1998–2002) to 130 (2003–2007) to 182 (2008–2012).” Their map (http://wwwnc.cdc.gov/eid/article/21/8/14-1878-f1) documents the exponential spread of LB over vast areas, graphically illustrating the growing threat of LB to more regions and more people.

Pfiefer (2016) (10) remarks on *Ixodes scapularis*, the ‘deer tick’ which transmits LB in North America: “In 1996, Ixodes scapularis, as it is known, had planted a foothold in 396 American counties. By 2015, the tick was established in 842 counties. This does not count another 578 counties—in all nearly half the continental U.S. total—in which the tick has been officially “documented.” ”

Borrelia species with known or suspected potential to cause LB

Borrelia Mayonii

The Centres for Disease Control and Prevention, 2016, describe a “New Lyme-disease-causing bacteria species discovered. *Borrelia mayonii* closely related to *B. burgdorferi*.
“[]. Until now, Borrelia burgdorferi was the only species believed to cause Lyme disease in North America.
“Scientists at the Mayo Clinic in Rochester, Minnesota, first suspected the possibility of new bacteria after lab tests from six people with suspected Lyme disease produced unusual results, according to the findings published today in Lancet Infectious Diseases. Additional genetic testing at the Mayo Clinic and CDC found that the bacteria, provisionally named Borrelia mayonii, is closely related to B. burgdorferi.
“This discovery adds another important piece of information to the complex picture of tickborne diseases in the United States,” said Dr. Jeannine Petersen, microbiologist at the Centers for Disease Control and Prevention.”(11)

Borrelia Bavariensis

Margos *et al* (2013) (12), state that *Borrelia bavariensis* is widely distributed in Europe and Asia: “Since the original description of Borrelia bavariensis sp. nov. in 2009, additional samples available from humans and ticks from Europe and Mongolia, respectively, have been used to further characterize Borrelia strains belonging to this group of spirochaetes that utilize rodents as reservoir hosts. These investigations suggested the presence of related strains in Europe and Asia and confirmed their status as representing a distinct species.”

Borrelia spielmanii

Maraspin, Ruzic-Sabljic and Strle (2014)(13) conclude in their case report:
"Our results corroborate previous findings that B. spielmanii is a cause of LB in Europe. Thus, in addition to the Netherlands (2), Germany (10), and Hungary (1), LB caused by B. spielmanii is also present in Slovenia."

Borrelia Bissettii

Rudenko *et al* (2016)(14) report on, "the first recovery of live B. burgdorferi sensu stricto from residents of southeastern USA and the first successful cultivation of live Borrelia bissettii-like strain from residents of North America. Our results support the fact that B. bissettii is responsible for human Lyme borreliosis worldwide along with B. burgdorferi s.s. The involvement of new spirochaete species in Lyme borreliosis changes the understanding and recognition of clinical manifestations of this disease."

Borrelia lusitaniae

While *B. lusitaniae* is distributed throughout countries in Europe and North Africa, it is believed to be the sole species of the Lyme borreliosis group in southern Portugal. Lizards of the family *Lacertidae* are thought to be important reservoir hosts of *B. lusitaniae*.(15)

De Carvalho *et al*(2008)(16) remark:
"We have described a vasculitis-like syndrome associated with the isolation of B. lusitaniae. Although the clinical presentation is not typical of Lyme borreliosis, this case had features suggestive of vasculitis, which has been described as one of the characteristic physiopathological aspects of this disease"

Borrelia Valaisiana

Diza *et al* (2004)(17) state:
"We detected *B. valaisiana* DNA in CSF of a patient with slow progressive spastic paraparesis, which suggests that this microorganism might be the causative agent of the disease. Nucleotide sequence information of *Borrelia* strains from clinical cases and ticks from different countries will elucidate the molecular epidemiology of the disease."

"The pathogenic capabilities of *B. valaisiana* are still uncertain; it has been detected by PCR and restriction fragment length polymorphism analysis in skin biopsy specimens from two erythema migrans patients and from patients with mixed infection (erythema migrans and acrodermatitis chronica atrophicans) (4). Indirect evidence suggests that B. valaisiana is involved in some chronic clinical manifestations (8)."

Reference 8 above is: Ryfell, *et al* (1999)(18), which states:
"Our results suggest an organotropism of *Borrelia* species and provide some evidence of a pathogenic potential of *B. Valaisiana* in humans."

Schwab *et al*, (2013)(19) state in *Borrelia valaisiana Resist Complement-Mediated Killing Independently of the Recruitment of Immune Regulators and Inactivation of Complement Components*:

"In conclusion, we demonstrated that B. valaisiana isolates differ in their susceptibility to human serum, thus providing some evidence that in particular serum-resistant isolates might cause Lyme disease. Contrary to our expectations, certain B. valaisiana isolates appear to possess different molecular mechanism(s) to inhibit complement activation, independently of the recruitment of complement regulators or by inactivation of central complement components. Even though that we are currently unable to decipher the precise molecular mechanism, it is tempting to speculate that B. valaisiana ZWU3 Ny3 expresses an outer surface protein that directly interacts with components of the complement system to inhibit complement activation. Further investigation is required to identify potential complement inhibitory protein(s) of this particular borrelial strain."

Cooper *et al*, (2001)(20) tested 75 ticks taken from wild animals in SW England. 41% tested positive for the presence of *borrelia* DNA. 34% of these were also positive for *Borrelia valaisiana*, considerably more than double the prevalence of this species in the rest of Europe.

Conclusion

In view of the spreading areas endemic for Lyme borreliosis and the diversity of borrelia species which pose a threat to humans; restricting Lyme borreliosis to just 3 of those species would inevitably fail to protect UK residents.

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