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Babesiosis: Analysis of the Evidence for Infections in the United Kingdom

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Abstract: Human babesiosis is caused when erythrocytes are invaded by *Babesia*. Infection can occur from the bite of an infected tick, blood transfusion or congenitally. Issues related to the infecting species, symptomology and testing technology are discussed and the implications of accurate incidence and prevalence of the disease discussed. Human babesiosis is considered to be relatively rare in the UK. With a considerable number of non-specific symptoms and diagnostic testing limitations, it is probable that true positives are being missed. Based on co-infection data for *Borrelia* and *Babesia* from Rhode Island and Connecticut, and on *Borrelia* seropositivity data from northeastern France, the prevalence of babesiosis in those aged under 35 years, 35 to 44 years, 45 to 54 years and 55 years and over would be expected to be 0.6%, 1.8%, 2.8% and 3.5%, respectively. Based on the prevalence of infections in ticks and canines and a disease model previously published, it is estimated that the UK incidence of human babesiosis is likely to be approximately 18,500 cases per year.

Keywords: *Babesia*, *Babesia venatorum*, lyme disease, coinfection, blood transfusion, serology testing

Introduction

The *Babesia* parasite is named after the Romanian physician and scientist Victor Babeş who, in his 1888 paper entitled "Sur l'hémoglobinurie bactérienne du bœuf", described the micro-organism in erythrocytes of cattle affected by febrile haemoglobinuria.[1] The bovine disease has various names including red water fever and has caused serious economic loss in many parts of the world.

The first identification of *Babesia* (*Piroplasma divergens*) in the UK was in 1911 by M'Fadyean and Stockman in cattle,[2] and the first case of human babesiosis in the UK was reported in Scotland in 1979.[3] There are more than 100 *Babesia* species known to infect mammals and birds,[4] with the *Ixodes ricinus* tick being the major carrier in Europe. A study by Bajer and Dwużnik-Szarek summarised information from 129 papers published over a 20-year period up to 2021 in which *Babesia* species were identified in ticks and GenBank molecular data.[5] Data for common European/UK *Ixodes* tick species demonstrated a prevalence of infection ranging from 0.5% in Denmark to 51% in Austria. There were seven species identified and other unnamed species that cause human babesiosis, with *B. divergens, B. microti* and *B. venatorum* the most common. Young et al listed over 1300 papers relevant to human babesiosis, including 11 with UK-specific data.[6] The most recent UK investigations identified a *Babesia* species (Clade X) in Scotland.[7] With more than 10 species and subspecies present in the UK and no published data on testing-accuracy for these, nor any surveillance data on human infections, the risk of infection and current incidence in the UK is unknown.

Symptoms and Coinfections

Babesia infections cause a wide range of symptoms including fatigue, headaches, chills, muscle and joint pains. These can vary from very mild to severe and can persist and be fatal. Whilst severe *Babesia* disease in the past has been associated with splenectomised patients, a recent paper highlights the occurrence of a "polymorphic persistent syndrome" including neurological and cognitive disorders with a positive serology and PCR for *Babesia divergens* in an

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immunocompetent, un-splenectomised patient.[8] The symptoms are very similar to those of Lyme disease (LD).[9] Differences between LD and Babesia symptoms have been described with "air hunger", chest pains, sweats and hip pains described.[10] Swanson et al, in a paper titled "Coinfections Acquired from Ixodes Ticks" give extensive data and references of humans multiply infected by pathogens from tick bites.[11] There are many reports of patients diagnosed with Lyme disease and simultaneously infected with *Babesia* parasites.[12–15] Increased symptom severity when *Borrelia* and *Babesia* infections occur simultaneously has been documented.[16] Djokic et al demonstrated that *B. microti* subverts adaptive immunity and enhances Lyme disease severity[17] and the number of symptoms and duration of illness are greater when coinfected by *Babesia* and *Borrelia*.[18]

In the US, where babesiosis is a notifiable disease in some States, during the years 2010 to 2016 there were 7818 patients admitted to hospitals with a diagnosis of babesiosis.[19] Of these, 38% were considered to have a major or extreme risk of death, while 25% were positive for Lyme disease. The authors state that during the period 2006 to 2017 Medicare insurance claims increased from 4/100,000 to 9/100,000. This represents an incidence for insured individuals of 0.009%. If this reflects the incidence for the general public there would be approximately 31,500 cases of babesiosis in the US in 2017.

Testing

Traditionally, detection of *Babesia* was carried out using blood smear microscopy; however, availability and sensitivity issues make this impractical for general medical diagnosis.[20]

Research projects are conducted using laboratory-prepared polymerisation chain reaction (PCR) tests, which are designed to detect target species of pathogens and have low or no sensitivity for non-target species.[20,21] A test kit developed for *B. microti*, which is prevalent in the US, is in use in the UK. However, European human babesiosis may result from multiple zoonotic species, with the most common *Babesia* species being *B. divergens, B. microti* and *B. venatorum*.[22] The inadequacy of PCR testing for the commonest *Babesia* species is exemplified by a recent report of a splenectomised patient in France suffering from pyrexia, dyspnoea and jaundice who initially tested negative for babesiosis with routine *B. divergens* and *B. microti* PCR; it turned out that he was infected with *B. crassa*.[23]

There are few commercially available test kits for European *Babesia* species and there is a need for high sensitivity rapid turnaround diagnostic kits for human samples to avoid missed diagnosis.[24] A Swedish group has recently developed an enzyme-linked immunosorbent assay–based methodology for routinely assessing human blood samples for levels of anti–*B. divergens* immunoglobulin G antibodies, which would offer a commercially available and less subjective alternative to the currently used indirect fluorescent antibody assays.[25] As babesiosis evolves, it is important to bear in mind the possibility that hitherto unsuspected species of *Babesia* may cause human babesiosis. For example, based on the findings from a one-day clinic, which took place in Ontario, in 2021 it was announced that *B. odocoilei* is also pathogenic to humans.[26] Interestingly, the inadequacy of PCR-based diagnostics in respect of the detection of both coinfections and novel species has been put forward as a reason for moving to next-generation sequencing methods for more accurate diagnostics.[27]

The incidence of *Babesia* infection in the US and the potential impact on health and health services is significant. The transmission of the disease by infected blood during transfusions is sufficiently high that screening of donor blood is considered to be necessary in the US.[28] The first laboratory to implement donor screening reported no cases of transfusion-transmitted babesiosis.[29] A recent Chinese murine study emphasised the risk of transmission of babesiosis by transfusion of blood containing low-density *B. microti* and recommended that "Babesia detection should be considered … as a mandatory test before blood donation or transfusion".[30]

Prevalence

Recently, Wilhelmsson et al reported that of a group of nymphal *Ixodes ricinus* ticks removed from humans in Sweden, 3.1% were PCR positive for *Babesia* species.[31] Also, the 2024 study by Jaenson et al based on the analysis of 168 papers on *Babesia* and *Borrelia* infection data determined that testing for *Babesia* species was rarely carried out in Europe and was a neglected public health issue.[32] A 2021 systematic review and meta-analysis of the global distribution of *Babesia*, based on over 100 studies published between 1985 and 2020 (inclusive), estimated a global pooled prevalence of 2.1% *Babesia* species in questing ticks.[33] More recently, a study of ticks collected from 170 humans in the Lombardy region of

northern Italy found that 7.6% were positive for *Borrelia* species and 0.6% for *B. venatorum*.[34] The presence and prevalence of *Babesia* species in the UK have been documented in a number of reports.[35–40] However, again these relate to animal (including tick) infections and not to human infections.

Recent studies of patients diagnosed with Lyme disease have shown that *Babesia* is a common co-infection, with 16.3% of patients positive in a Swedish study and 11.5% in Germany.[41,42] Krause et al found in a survey of 1156 human subjects based in Rhode Island and Connecticut that 8.4% were positive for *Borrelia* infections and of these 14% were positive for *Babesia* species.[18] If a similar proportion holds in countries neighbouring the UK, then, using *Borrelia* seropositivity figures published for northeastern France, the prevalence of babesiosis in those aged under 35 years, 35 to 44 years, 45 to 54 years and 55 years and over would be expected to be 0.6%, 1.8%, 2.8% and 3.5%, respectively.[43] Interestingly, this range of 0.6% to 3.5% includes the reported prevalence of 0.71% for seropositivity for *Babesia* in an adult patient cohort at an infectious disease clinic in another UK neighbour, namely Ireland.[44]

A study of 278 British veterinary practices, carried out in 2016, reported that 601 out of 1855 cats had attached ticks, and of these ticks, 0.37% were positive for *B. venatorum* and 1.8% positive for *Borrelia* infections.[40] This gives a *B. venatorum* infection rate of 20% of the rate of *Borrelia* infections. The percentage of Lyme disease patients coinfected with *Babesia* from the three studies of human infection is 14.1%. Official data for the incidence of Lyme disease in the UK is in the low thousands per year; however, these data are only for cases reported by the Rare and Imported Pathogens Laboratory. They do not include those cases diagnosed by clinicians and those undiagnosed or misdiagnosed. An estimate of annual incidence and prevalence of Lyme disease for the UK and many other countries is derived from an accurate model published in 2021.[45] The model uses the number of cases of Lyme disease diagnosed in Germany in the years 2007–8. It was validated against data published by the Centers for Disease Control and Prevention for the US. Using the model data for an estimate for the incidence of Lyme disease in the UK gives an estimate for human babesiosis of 18,500 cases per year.

It is not only feline ticks which carry *B. venatorum* in the UK. *B. venatorum* has now been found to be present in the sheep population of the UK, thereby presenting an infectious risk to humans who work, live or hike in areas frequented by sheep.[35] Similarly, 2.4% of ticks from migratory birds captured in south-eastern Sweden have been found to be positive for *Babesia*; three species were identified, namely *B. venatorum* (58%), *B. microti* (38%) and *B. capreoli* (4%).[46]

Discussion

Babesiosis is beginning to be recognised as a cause of serious illness not only in immunosuppressed patients but also otherwise healthy subjects. The symptoms are non-specific and closely match those for other diseases, making differential diagnosis difficult. The tests used for *Babesia* frequently target non-native species in the UK. Also, there are no published data of the accuracy of the tests (sensitivity and specificity). The seriousness of the disease is recognised in the US, where routine testing of blood donations for *Babesia* is carried out and the need for improved testing is being pursued. There should be increased recognition of this disease in the UK with the use of tests capable of detecting the *Babesia* species present here. A call for national surveillance of ticks and tickborne infections, both bacterial and viral, has been made by a UK group and should be given full support.[47]

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