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Tick-borne diseases in the North Sea Region - a comprehensive overview and recommendations for diagnostic, treatment and management strategies



Interreg
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NorthTick

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Preface

NorthTick is a project on ticks and tick-borne diseases co-funded by the European Union through the European Regional Development Fund and the North Sea Region Programme 2014 – 2020 (1). This management summary is performed as part of NorthTick. Eleven beneficiaries from seven different countries: Denmark, Sweden, Norway, Germany, Belgium, Scotland (United Kingdom) and the Netherlands, are involved in the project.

Ticks are the most important vectors for a multitude of human and veterinary pathogens in Northern Europe. The distribution of ticks is expanding and tick-borne diseases constitute growing health risks (1, 31). The number of people and animals afflicted by tick-borne diseases are on the rise. The reasons are complex. They include climate changes, increased urbanisation and other human influences on the ecosystems.

While the probability of getting a tick-borne disease is relatively low for an individual, the health problems and economic consequences this may have for affected persons, and the burden this represents for society, can sometimes be substantial. It is challenging for health services and authorities to be updated on the best practise strategies for prevention and diagnostics, treatment and management of tick-borne diseases, and give appropriate and quality assured information to a concerned public. The internet's emerging role as a primary source of health advice for many people should not be underestimated. Many websites give unreliable information about ticks and tick-borne diseases (2-4).

NorthTick aims to meet these challenges by providing a multi-disciplinary and transnational joint effort to improve public health service delivery regarding risk assessment, efficient preventive measures, optimal diagnostic strategies and best patient management for tick-borne diseases.

To this end, existing guidelines in the North Sea Region were compared (14, 15, 21-30, 34-38). Local experts were consulted online, in face-to-face meetings, and working groups.

Diagnostic and management strategies from each region involved are summarised. There are some minor differences, but mostly high degrees of overlap, from which clinically important recommendations are suggested. While physicians should consult national guidelines for diagnosis and treatment of patients suspected of having tick-borne diseases, and this document is not a clinical guideline, our goal is to provide a comprehensive overview of the diagnostics, treatment and management of tick-borne diseases, based on validated accumulated knowledge and common practices in the North Sea Region. This will help health care providers in the North Sea Region to provide the best possible information and care for patients with, or with suspected tick-borne diseases.

Possible tick-borne diseases should be confirmed or refuted as quickly as possible. That will improve patient safety and care. This work may help reduce time from onset of symptoms to proper diagnoses and treatment, as well as reducing misdiagnoses and unnecessary use of antibiotics. Thereby, the number of persons having long-term complaints after tick-borne diseases can be reduced.

This draft document has been discussed between partners, stakeholders and target groups involved in the NorthTick project before publication of this final version.

The document uses the term borreliosis, not Lyme borreliosis. Further, neuroborreliosis, borrelia arthritis, and borrelia carditis are used instead of Lyme neuroborreliosis, Lyme arthritis and Lyme carditis.

List of abbreviations

ACA	Acrodermatitis chronica atrophicans
B	Borreliosis
BA	Borrelia arthritis
Bb	Borrelia burgdorferi
BC	Borrelia carditis
b.i.d.	bis in die (twice a day)
CNS	Central nervous system
CSF	Cerebro spinal fluid
ELISA	Enzyme-linked immunosorbent assays
HSL	Health Services Laboratories
IFA	Indirect immunofluorescent-antibody test
ME/CFS	(Myalgic Encephalopathy/Chronic Fatigue Syndrome
NB	Neuroborreliosis
NSR	North Sea Region
PCR	Polymerase chain reaction
q.d.	Once daily
RIPL	Rare and Imported Pathogens Laboratory
Sl	Sensu lato (a collective term for several species)
Spp.	Species pluralis (Latin abbreviation for multiple species)
TBD	Tick-borne diseases
TBE	Tick-borne Encephalitis
t.i.d.	three times a day
UK	United Kingdom

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Background

Diagnosing and treating tick-borne diseases is a topic of discussion. Despite the existence of several European quality assured guidelines and recommendations, there are divergent explanatory models and treatment recommendations for tick-borne diseases, especially presented at different websites (2-4). Such divergences may lead to uncertainty, diagnoses made on inadequate or inappropriate bases, and use of unrecommended diagnostic and treatment strategies (5-10, 39). Diagnoses of tick-borne diseases may be delayed or missed, or wrong diagnoses may be given. This implies possibilities for unfortunate outcomes after infections, or may result in over-diagnosis and over-treatment. Patients often describe that they are sent around in the health care system, from one specialist to another, and the confirming or refusal of a correct diagnosis might take months or even years. It is common that wrong diagnoses of borrelioses are based on findings by serology only.

Some doctors may choose to treat, or not follow guidelines, in order to be on the “safe side” when dealing with possible tick-borne diseases. The diagnosis of e.g. neuroborreliosis can be demanding, and includes a lumbar puncture according to European guidelines. New studies from specialised clinics where doctors refer patients with health complaints after possible tick-borne disease, show that a substantial number of these patients have other diagnoses than tick-borne diseases, such as multiple sclerosis or other chronic neurological or systemic diseases (32). Practitioners must be aware that over-diagnosis and over-treatment is not only expensive for patients and the healthcare system, but may, in some cases, result in serious, sometimes deadly, complications (40-44).

In recent years, some users of North Sea Region health services have experienced inadequate diagnostic help and treatment for tick-borne diseases (5, 11). Different groups have raised their voices in several European countries asking for more focus on prevention, recognition, diagnosis, treatment and follow-up of long-term symptoms and signs that they attribute to tick-borne diseases. Some patients fear they have a tick-borne disease of which they do not get proper, or may be denied, assessments of in the health care system. Other patients are offered unvalidated diagnostics and therapies by some clinics.

A Nordic initiative

In 2013, the Norwegian Directorate of Health was given an assignment to improve health-care for persons with long-term health problems attributed to diseases caused by tick-bites. The process of that work was based on dialogue with patient organisations, the Norwegian National Advisory Unit on Tick-borne Diseases and the Norwegian, Swedish and Danish Institute of Public Health. The aim was to establish a Nordic consensus on the diagnosis, treatment and follow up persons with tick-borne diseases. The first Nordic consensus meeting was held in 2015, where more than 40 experts on tick borne diseases participated, comprising clinicians from relevant medical fields, researchers, patient organisations, health authority personnel and public health representatives.

A report on the Nordic consensus on the assessment and follow-up of persons with long-term health problems attributed to diseases caused by tick-bites, was published in 2020 (5). A summary of the recommendations was published in 2021 (12).

The North Sea Region initiative

The intention of making a management summary for tick-borne diseases - through the NorthTick project - is to provide patients with tick-borne diseases proper diagnostics, treatment and follow-up independent of where they live in the North Sea region. A special focus is on persons with long-term symptoms.

Two major groups of patients with long-term symptoms stand out:

- 1) Patients correctly diagnosed and treated for tick-borne diseases. After antibiotic therapy, some still experience symptoms that might be long lasting (77). Many of them worry that they may have a persistent, active infection, despite having received treatment according to guidelines.
- 2) Patients with long-term complaints and a suspicion of tick-borne diseases, in which the diagnoses cannot be confirmed. While some of these patients may actually have tick-borne diseases and insufficient

diagnostic workups, others obtained the diagnosis of tick-borne disease in a non-justified manner (e.g. based on non-validated laboratory tests, or unspecific findings, or long lasting symptoms only). Most patients want a definite diagnosis, and in order to find answers/explanations and treatment for their symptoms, some patients indirectly feel forced to seek healthcare in clinics that are not parts of the ordinary healthcare system (32).

Process for this document

This North Sea Region initiative is led by:

- Randi Eikeland, Neurologist, PhD, MD, leader of Norwegian National Advisory Unit on Tick-Borne Diseases, Sørlandet Hospital, Kristiansand, Norway, and associate professor at Department of Health and Nursing Sciences, University of Agder, Grimstad, Norway.
- Anna J Henningsson PhD, MD, clinical microbiologist, senior associate professor at Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden, and medical chief officer of Department of Clinical Microbiology in Jönköping, Region Jönköping County, Linköping University, Linköping, Sweden.
- Anne-Mette Lebech, PhD, MD, infectious diseases specialist, associate professor at Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen.

They were also engaged in the Nordic consensus-work on tick-borne diseases (5).

The process of making this NorthTick recommendations report, engaged working groups on:

1. Surveillance
2. Diagnostics
3. Treatment and follow-up

First, all leading representatives from the seven North Sea Regions provided current national guidelines, recommendations and practice experiences in the field. Next, this was presented in a workshop with an invited group of experts from the North Sea region. The group was multidisciplinary with members having experience in fields of clinical and diagnostic work, public health, and recommendations and guideline production.

A draft document of January 12th 2022 has been assessed by involved stakeholders, and discussed in a meeting at the NordTick conference June 15th 2022.

The document presents management summaries and recommendations concerning tick-borne diseases in the North Sea Region, where feedback from the above mentioned processes are incorporated.

Surveillance, tick-borne diseases, North Sea Region

An overview of the surveillance of tick-borne disease in the different North Sea Region countries is presented in Table 1. In 2018, the European Commission included neuroborreliosis on the list of diseases under epidemiological surveillance. In some of the North Sea Region countries, specific clinical presentations of borreliosis are notifiable, while in others, only specific regions within the country have listed borreliosis as a mandatory notifiable disease. In Belgium, none of the clinical presentations of borreliosis are notifiable. Making a disease notifiable is one way of surveilling a disease; other ways are e.g. by different registers, laboratory results and sentinels.

Tick-borne encephalitis (TBE) has been a notifiable disease in the European Union since 2012. However, the surveillance strategies differ within the North Sea Region. In Germany, Norway and Sweden, TBE is mandatorily notifiable, while in Belgium, Denmark and the Netherlands it is not. However, in the latter countries, the National Health Institutions register TBE cases.

The prevalence of other tick-borne diseases, caused by pathogens such as *Anaplasma phagocytophilum*, *Rickettsia* spp., *Bartonella henselae*, *Francisella tularensis*, *Babesia* spp., *Neoehrlichia mikurensis* and *Borrelia miyamotoi*, varies greatly between the countries in the North Sea Region.

Table 1: Surveillance of tick-borne diseases in North Sea Region

Country	Borreliosis	Tick-borne encephalitis	Other tick-borne diseases
Belgium	Different sources of information used for different presentations of borreliosis (EM through sentinel network GPs, lab surveillance, Hospital data)	Few imported cases yearly and sporadic autochthonous cases. Surveillance based on laboratory reports (one main reference centre)	Surveillance mainly through national reference centres Rickettsiosis and Tularaemia are mandatorily notifiable
Denmark	Neuroborreliosis has been notifiable since 1991	Not notifiable. TBE cases are monitored by the Department of Virology at the National Institute for Health Data and Disease Control (Statens Serum Institut) since 2000	Other TBDs are not notifiable
Germany	Notifiable in 9 of 16 states. Erythema migrans, neuroborreliosis and borrelia arthritis are notifiable	Comprehensive, mandatorily notifiable	According to German Infection Protection Act (IfSG), direct or indirect evidence of <i>Francisella tularensis</i> - if it indicates an acute infection is notifiable. Other TBDs are not notifiable
Netherlands	Episodic epidemiological research to estimate prevalence by the National Institute for Health and Environment (RIVM) Not notifiable	Not notifiable. The National Institute for Health and Environment (RIVM) registers TBE cases.	<i>Anaplasma phagocytophilum</i> and <i>Neoehrlichia mikurensis</i> and <i>Rickettsia</i> spp. are not notifiable <i>Babesia</i> spp. contact relevant authorities due to the rarity
Norway	Disseminated infection is notifiable. Norwegian Surveillance System for Communicable Diseases (MSIS) since 1997	Comprehensive, mandatorily notifiable.	Cases caused by <i>Rickettsia</i> spp. and <i>Francisella tularensis</i> , are notifiable
Sweden	Not notifiable. Research to estimate incidence	Comprehensive, mandatorily notifiable	Not notifiable *
Scotland (UK)	Borreliosis is not a notifiable disease but <i>Borrelia burgdorferi</i> (Bb) is a notifiable organism	One case in Scotland in 2022, two cases in England during 2019 and 2020.	Tularaemia is a notifiable disease, <i>Francisella tularensis</i> and <i>Rickettsia prowazekii</i> are notifiable organisms

* Cases of anaplasmosis, rickettsiosis, neoehrlichiosis, babesiosis and *Borrelia miyamotoi* disease are reported in scientific literature.

Recommendations

Updated data on incidence of disseminated borreliosis, TBE and other potentially serious tick-borne diseases can improve awareness in the field. Data can be collected from laboratory or surveillance systems. Such data can monitor trends and identify population at risk, increase awareness of tick-borne diseases and contribute to better understanding and research regarding infectious diseases - in particular occurrence and cause of infections. Thus, it may contribute to earlier diagnoses, reduce misdiagnoses, and prevent long-term impacts of TBD.

Feedback to the report-draft of January 12th 2022:

From stakeholders and at the NorthTick recommendations meeting June 15th 2022, at Fevik, Norway: Make all cases of TBDs mandatory notifiable in the North Sea Region, is desired by some patient organisations.

As for surveillance of borreliosis, harmonization across countries on surveillance data for disseminated borreliosis (neuroborreliosis and borrelia arthritis), and on incidence of Erythema migrans is warranted. This can contribute to better understanding of the transmission of borrelia infections.

As for surveillance of tick-borne encephalitis, better identifications of geographical areas for transmission (risk assessments) can support recommendations for vaccination.

Diagnosics

Diagnoses of tick-borne diseases should be based on possible tick-exposure, the patients' medical history, clinical signs and symptoms, vaccine status, and interpretation of diagnostic test-results. Due to the sometimes non-specific nature of the different tick-borne diseases and their manifestations, alternative diagnoses should be considered, or ruled out. Where available, diagnostic tests used should be properly validated in a clinical setting. Immunocompromised patients are prone to acquire new and old tick-borne infections, show atypical symptoms and signs, and have more severe infections. Because such patients may test negative on serology tests, they may be in need of supplementary diagnostic tests to avoid missing or delaying correct diagnoses (75).

Borreliosis

Countries in Western Europe have a large variance in the incidence rates of borreliosis. A publication estimating local and disseminated borreliosis, estimates the highest incidences in southern Sweden with 464/100 000 and the lowest in Italy of 0.001/100 000 (56). The unweighted mean for the included data in that paper provided an incidence rate of 56.3/100 000 persons per year, equating to approximately 232 000 cases in 1 year throughout the region. The calculated population-weighted average incidence rate for the regional burden of B in Western Europe is 22.05 cases per 100 000 person-years (66). The number of borreliosis cases in Europe has increased steadily over the last two decades, according to WHO Europe (56).

The skin rash Erythema migrans (EM) is a clinical diagnosis. EM is the most common local manifestation of borreliosis. It is based on possible tick-exposure, medical history, clinical signs and symptoms. Antibody testing (serology) is not recommended because the production of antibodies is relatively late and the test thus can be false negative early in the disease. Alternatively, when the skin lesion is less evident, or is a sign of a different disease, the serological test may be positive due to former exposure to Borrelia bacteria from earlier tick-bites. Cases of erythema migrans often remain seronegative after treatment (19). In a study by Leeflang et al, on serological tests for borreliosis in Europe, sensitivity summary estimates were 50% (95% CI 40% to 61%) for EM (46).

Therefore, according to the recommendations from all countries in the North Sea Region, typical EM is a clinical diagnosis that should promptly be treated without prior laboratory tests.

Similar clinical assessments as for EM go for borrelia lymphocytoma, which is a relatively rare symptom of borreliosis. It accounts for approximately 2% of all borreliosis cases, and is most common in children. A typical borrelia lymphocytoma appears on the earlobe as a small red/purple swelling (or as a reddish streak on top of the ear cartilage). The swelling may be tender. The size is typically between 0.5 to 3 cm. Lymphocytoma can also appear on the nipple or on the genitals/scrotum.

In our working process, we identified that all countries use Enzyme-linked immunosorbent assays (ELISAs) as screening tests for detection of *Borrelia burgdorferi* specific IgG and IgM antibodies. The value of IgM, especially in serum samples, is questioned in Sweden and Denmark (20). Scotland experiences many positive IgM (ELISA and immunoblot) tests, where many appear to be false positive (negative IgG in repeat serology over 4-6 weeks, while IgM positivity persists).

Some countries use immunoblot to confirm equivocal/positive ELISA results. Sweden and Norway use it on selected cases only. In the Netherlands, a modified two-tier testing - in which a second ELISA is used as a confirmatory test - has been under investigation (47). Immunoblot is not used in Denmark, because the two-tier approach may suffer from a loss of sensitivity depending on the individual sensitivities and specificities of the applied test combinations. This is especially true for localised and early phases of borreliosis with a less pronounced immune response directed against a narrower spectrum of specific and non-specific *Borrelia* antigens. (19).

PCR is offered by all countries specifically for skin biopsies, joint fluid aspirates, and to a lesser extent Cerebro spinal fluid (CSF) - due to low diagnostic sensitivity of PCR in CSF.

In neuroborreliosis (NB), antibody index calculations are performed in all the North Sea Region countries to prove a higher antibody concentration in CSF than in serum. All countries offer CXCL13 testing in CSF as a complementary method to specific antibody index.

Table 2: Diagnostic tests for borreliosis

Country	Diagnostics borreliosis
Belgium	<ul style="list-style-type: none"> • Two tier test including Western Blot (WB) • CSF pleocytosis, PCR, genospecies, CXCL13
Denmark	<ul style="list-style-type: none"> • EM no serology • Other clinical manifestations: ELISA – WB not performed • NB: Intrathecal <i>Borrelia</i> specific IgM/IgG index (Serum/CSF) and CXCL13 in CSF • Second line for ambiguous cases: PCR (skin, joint fluid) • Histology: Lymphocytoma, ACA
Germany	<ul style="list-style-type: none"> • EM no serology, all other manifestations confirmation by serology • Two Tier tests: ELISA/CLIA, if reactive with confirmatory immunoblot • Others: Histology, PCR (skin, synovial fluid) • NB: Bb-specific CSF-serum antibody index, CSF parameters, (CXCL13) • Second line for ambiguous cases: PCR/culture (skin, CSF, joint fluid) • Positive culture confirmed with molecular/biological methods
Netherlands	<ul style="list-style-type: none"> • EM no serology • Serology: ELISA and immunoblot (Standard two-tier testing) • PCR: puncture or biopsy of affected organs (joint, skin and in particular cases CSF) • Culture: puncture or biopsy of affected organs (joint, skin and in particular cases CSF). Only available in one academic centre. • Immunologic: CXCL13 in CSF additional in NB • Cellular tests not recommended (under investigation)
Norway	<ul style="list-style-type: none"> • Antibody testing <ul style="list-style-type: none"> ○ Serum: IgG and IgM ELISA (Blot on possible false positive) ○ CSF: IgG, IgM, (Immunoblot IgG), Index IgG, IgM, (CXCL13) • PCR testing <ul style="list-style-type: none"> ○ Synovial fluid ○ Skin (atypical rash) ○ CSF (children, short disease duration) ○ Blood (immunosuppressed)
Sweden	<ul style="list-style-type: none"> • ELISA IgG and IgM, immunoblot in selected cases (IgM is questioned) • NB: AI, CSF cell count, CXCL13 in some laboratories • PCR: arthritis, ACA, sometimes CSF • Histology: lymphocytoma, ACA • Culture: National reference laboratory, performed for research and epidemiological purposes only

Scotland (UK)	<ul style="list-style-type: none"> • Screening EIA with confirmatory immunoblot if positive/equivocal • NB: CSF/serum pair for antibody index calculation and CSF cell count and CXCL13 • PCR-CSF, joint fluid and skin
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Recommendations

There are two main differences in diagnosing borreliosis concerning 1. Antibody testing and 2. Two-tier testing:

- Some measure both *B. burgdorferi* IgM and IgG antibodies in serum, while others only measure *B. burgdorferi* IgG (or the laboratories only provide clinicians with the IgG results)
- Some perform both ELISA and immunoblot, others perform ELISA(s) only

The diagnostic strategy concerning antibody testing ought to be uniform across Europe, based on updated knowledge.

Important:

- Interpret IgM, especially in serum samples, with caution. Many are false positive (negative IgG in repeat serology over 4-6 weeks, while IgM positivity persists).
- A diagnosis of borreliosis cannot be based on serology alone. The diagnostic processes for tick-borne diseases are based on possible tick-exposures, the patients' medical history, clinical signs and symptoms, vaccine status, and interpretation of diagnostic test-results.
- Borrelia-specific IgG-antibodies is mandatory in late disease (can be exceptions in immunocompromised patients).
- Results of lumbar puncture is needed for diagnosing neuroborreliosis. Neurological symptoms, inflammatory lymphocytic cells and detection of Borrelia-specific antibody production in CSF, are necessary for the diagnosis of definite neuroborreliosis. Antibody Index is to be calculated if *B. burgdorferi* specific antibodies are detected in both serum and CSF.

Borrelia miyamotoi

Borrelia miyamotoi disease is rare in the North Sea Region, but one should be aware of the possibility in patients with an acute febrile illness after a tick-bite, or with a meningoencephalitis in immunocompromised patients. All seven countries can test for *Borrelia miyamotoi*. Five countries use PCR, and two countries use experimental serology in addition to PCR. Culture of the organism from patient blood has also been tested(48), but requires special medium, is labour intensive, might take weeks for a definite result, and is reserved mainly for research purposes. Direct visualisation of spirochetes in patient blood, in contrast to other relapsing fever *Borrelia* species which have higher spirochete levels in blood, has no place in routine laboratory practice either (49). Serology requires further research and validation before it can be routinely used in clinical practice.

Serology could be of interest in patients that present after a few weeks of symptoms, or outside of a febrile episode. Antibodies from *B. miyamotoi* disease patients may cross-react in commercially available borreliosis serological tests, although these tests may also be negative (70). *B. miyamotoi* serology is currently mainly based on GlpQ (Glycerophosphodiester Phosphodiesterase), a protein that is present in all relapsing fever *Borrelia*, but not in *B. burgdorferi* sensu lato. GlpQ has been studied as a standalone antigen or in combination with other antigens, or whole cell lysate Western blots. In patients with acute symptoms and/or fever (when spirochetemia is expected), PCR on blood is the preferred diagnostic test, and in patients with a meningitis or meningoencephalitis PCR on CSF.

Table 3: Diagnostic tests for *Borrelia miyamotoi*

Country	<i>B. miyamotoi</i> tests
Belgium	<ul style="list-style-type: none"> • PCR
Denmark	<ul style="list-style-type: none"> • PCR (only on special request)
Germany	<ul style="list-style-type: none"> • PCR
Netherlands	<ul style="list-style-type: none"> • Pan-relapsing fever <i>Borrelia</i> PCR (detecting all relapsing fever <i>Borrelia</i> genospecies) or <i>B. miyamotoi</i> specific PCR for blood and CSF • Serology is experimental of nature and is thus not routinely used. It is based on GlpQ with or without other <i>B. miyamotoi</i> antigens (45)
Norway	<ul style="list-style-type: none"> • PCR for blood and CSF
Sweden	<ul style="list-style-type: none"> • PCR for blood and CSF
Scotland (UK)	<ul style="list-style-type: none"> • Pan-borrelia PCR (detecting both relapsing fever and other borrelia genospecies) for blood and CSF

Recommendations

For clinical diagnostics use PCR (serology when made available).

Tick-borne Encephalitis (TBE)

Approximately 5 000 - 12 000 cases of TBE are reported in Europe each year (57).

TBE virus can be transmitted from the *Ixodes ricinus* tick (in the Baltics and Finland also from *Ixodes persulcatus*), shortly after a tick-bite. Symptoms can arise 1-2 days, usually 4-8 days, after the tick bite. The incubation period is 2-28 days. Consumption of unpasteurized dairy products is also a possible way to transmit TBE infection. TBE vaccines are available.

Suspect TBE in North Sea Region endemic areas where symptoms appear shortly after a tick bite in patients presenting biphasic patterns of fever, headache and gastrointestinal symptoms (which are all uncommon in borreliosis).

All countries in North Sea Region except Scotland offer testing with ELISA, PCR or both. Although testing is not available in Scotland, samples can be referred to the Rare and Imported Pathogens Laboratory (RIPL) in England. The situation for Scotland will be reviewed if there is clinical need for testing.

The different diagnostics for TBE-viruses used in the different countries are listed in Table 4.

Table 4: Diagnostic tests for TBE

Country	Diagnostics
Belgium	<ul style="list-style-type: none"> • Serology: ELISA (EUROIMMUN kit). Neutralisation test on equivocal and positive results
Denmark	<ul style="list-style-type: none"> • Serum and CSF : Specific TBE IgG/IgM antibodies • TBE Real time RNA PCR in serum, CSF
Germany	<ul style="list-style-type: none"> • Serology: ELISA, indirect immunofluorescent-antibody test (IFA), NT TBE IgG/IgM antibodies (Specific antibodies can only be tested by NT test which cannot distinguish between IgG and IgM; ELISA and IIFA are not specific (means show cross reactions with other flavivirus antibodies) • Intrathecal TBE-specific IgM and/or IgG antibodies, or NS1-IgG (antibodies against the TBEV-NS1 protein show high specificity without any cross-reactivity against other flavivirus) • TBE real time q RT-PCR in serum (in case of first viremic phase), CSF (in case of immunosuppression or immunodeficiency)
Netherlands	<ul style="list-style-type: none"> • Serology: ELISA (virus neutralization test upon indication –at RIVM, and EMC) • RT-PCR: blood (drawn during fever), CSF (RIVM)
Norway	<ul style="list-style-type: none"> • Serum: PCR if early, IgM, IgG • CSF PCR, IgM and IgG
Sweden	<ul style="list-style-type: none"> • IgM in single serum or elevation of IgG in paired sera by ELISA or lateral flow assay. Confirmation of IgM reactivities by the use of two independent tests is recommended • Suspected vaccination breakthroughs: paired CSF/serum samples, IgM in CSF
Scotland (UK)	<ul style="list-style-type: none"> • Not available in Scotland • England (RIPL): PCR and serology (serum and CSF)

Recommendations

For diagnosis, PCR test can be used in the first viremic phase of TBE, but in later phases serology is the preferred diagnostic test. If the test is taken shortly after onset of symptoms and comes out negative, repeat test if the suspicion of TBE still remains.

Other Tick-Borne diseases

These should be considered in patients where tick-borne diseases are suspected and borrelia or TBE are not confirmed, especially if there is fever of unknown cause. Be especially aware of uncommon tick-borne diseases in immunocompromised patients (61).

Human granulocytic Anaplasmosis (HGA)

Despite an increasing prevalence of HGA in animal hosts, human cases are not frequent, though maybe underestimated due to the nonspecific clinical signs (flu-like symptoms) (58).

All countries perform serology and PCR, except Scotland - performing PCR only. Belgium, Germany and the Netherlands also offer stained blood smears.

Antibody production may take 2-3 weeks to develop, thus serology may not be conclusive in early cases. However, serology in follow-up samples can confirm HGA. Cross-reactivity can occasionally occur between *E. chaffeensis* and *A. phagocytophilum*, and potentially also *Neoehrlichia mikurensis* (71).

Culture may require many days and is not widely available. PCR is recommended for acute cases, but sensitivity may vary.

Table 5: Diagnostic tests for HGA

Country	Diagnostics
Belgium	<ul style="list-style-type: none"> Real-time PCR & microscopic detection; in practice: mostly based on serology because late suspicion
Denmark	<ul style="list-style-type: none"> Serum IFA IgG (and IgM) PCR (unknown annual incidence in humans)
Germany	<ul style="list-style-type: none"> PCR (buffy coat) and stained blood smears acute phase; Serology (IFA): acute and convalescent So far no autochthonous cases
Netherlands	<ul style="list-style-type: none"> Serology: commercially available immunofluorescence assay PCR: blood (drawn during fever, experimental) Culture: from buffy coat Microscopy: blood smear, Giemsa
Norway	<ul style="list-style-type: none"> PCR (serology not available in public labs) Microscopy
Sweden	<ul style="list-style-type: none"> Serology (immunofluorescence assay (IFA) for IgG) PCR
Scotland (UK)	<ul style="list-style-type: none"> Scotland-PCR whole blood in acute phase (less than 4 weeks from onset) England (RIPL) -PCR and serology

Recommendations

To diagnose HGA, use PCR in the early phase of illness, then serology. If the test is taken shortly after onset of symptoms and comes out negative, repeat test if suspicion of Anaplasmosis remains. A moderate IgG level in a single serum sample is not enough for definite diagnosis of on-going anaplasmosis, and a follow-up serum should therefore be taken 4-6 weeks later to demonstrate an antibody increase.

Rickettsiosis

This paragraph does **not** cover the diagnosis of more exotic forms of rickettsiosis, for example from travellers (e.g. African tick-bite fever).

The incidence of rickettsioses acquired by tick bites in the North Sea Region is very low. So far, four tick-associated rickettsia species have been detected in the NSR: *Rickettsia slovaca* - the causative agent of TIBOLA (tick-borne lymphadenopathy), *R. helvetica*, *R. monacensis* and *R. massiliae*. They have unclear human pathogenicity, but are associated with unspecific febrile illnesses after tick bites.

Six countries can test for Rickettsia. Scotland sends all tests to RIPL in England. The Netherlands utilise serology, but not PCR (apart for research purposes) based on the presentation. Serology for Rickettsia - endemic in *Ixodes ricinus* (e.g. *Rickettsia helvetica* and *R. monacensis*) – cross-react with other spotted fever group (SFG) Rickettsia species (e.g. *R. conorii*). Serology is not useful for diagnosing acute illness; antibodies can take 10-14 days to develop.

Table 6: Diagnostic tests for rickettsioses

Country	Diagnostics
Belgium	<ul style="list-style-type: none"> • Serology and PCR
Denmark	<ul style="list-style-type: none"> • Serology IFA SFG-<i>Rickettsia</i> and <i>R typhi</i> IgM and IgG • PCR for eschar and enlarged lymphnodes
Germany	<ul style="list-style-type: none"> • Pan-<i>Rickettsia</i> serology and Pan-<i>Rickettsia</i> PCR • Serology (IFA) IgG from sera, plasma • PCR from eschar, ticks
Netherlands	<ul style="list-style-type: none"> • Serology: IFA or ELISA on SFG-<i>Rickettsia conorii</i>, high cross reactivity
Norway	<ul style="list-style-type: none"> • PCR (Pan-<i>rickettsia</i>) in blood, skin biopsy and CSF (Serology not available in public labs. Samples sent abroad if needed)
Sweden	<ul style="list-style-type: none"> • <i>Rickettsia helvetica</i>: serology (IFA) • PCR
Scotland (UK)	<ul style="list-style-type: none"> • Not available in Scotland • England (RIPL): IgG and IgM by IF. RT-PCR for eschar biopsy, CSF, swabs

Recommendations

To diagnose Rickettsiosis, PCR can be used in the early phase of illness, then serology. If the test is taken shortly after onset of symptoms and comes out negative, repeat test if the suspicion of rickettsiosis still remains. A moderate IgG level in a single serum sample is not enough for definite diagnosis of on-going rickettsiosis, and a follow-up serum should therefore be taken 4-6 weeks later to demonstrate an antibody increase. False positive IgM tests occur.

Neoehrlichiosis

The first European case of *Neoehrlichia mikurensis* (formerly known as *Candidatus N. mikurensis*) infection, was in a Swedish patient with chronic lymphocytic leukaemia, prolonged fever, erysipelas-like rash and thromboembolic complications, and recovered on doxycycline (63). One publication states that 18 cases have been reported from European countries until 2018 (62). However, a publication from 2020, summarises findings concerning 40 Swedish patients in the period 2009 – 2019 (71). As of January 12th 2022, that number is 83. *N. mikurensis* infections are mostly found in immunocompromised patients. Six countries can test for *N. mikurensis* with PCR. To date, there is no serological method available, but a protocol for development of serological assays is part of the NorthTick project (33).

Table 7: Diagnostic tests for Neoehrlichiosis

Country	Diagnostics
Belgium	PCR under development
Denmark	PCR blood. Only for research use
Germany	PCR in development
Netherlands	PCR experimental of nature
Norway	PCR blood, skin biopsy (in clinical use)
Sweden	PCR (in clinical use)
Scotland (UK)	Not available in Scotland (UK)

Recommendations

Keep the possibility of Neoehrlichiosis in mind in immunosuppressed patients with a history of tick-bites and unexplained fever. Especially consider when combined with thromboembolic events, or an unexplained tendency for blood clots. Do PCR.

Babesiosis

There are 39 clinically severe human cases published in Europe until 2021 (64).

All countries indicate that testing is available (combination of microscopy, serology and PCR). Microscopic diagnosis of babesiosis requires time and expertise. Thick blood smears can be difficult to interpret and should be performed only by experienced microscopists. In the setting of very low parasitaemia (particularly at the onset of symptoms), examination of multiple smears over several days may be required.

Serology should be interpreted with caution as rise in antibody titer can be delayed and may persist beyond resolution of infection, making it difficult to distinguish current from past infection. Cross-reactivity has been reported between *B. divergens* and *B. divergens*-like organisms and between *B. divergens* and *B. venatorum* (13). PCR is useful in the setting of low-level parasitaemia (e.g., in asymptomatic carriers/at the onset of symptoms). It also enables species identification and parasite quantification.

Table 8: Diagnostic tests for babesiosis

Country	Diagnostics
Belgium	<ul style="list-style-type: none"> • Combination of microscopy and PCR
Denmark	<ul style="list-style-type: none"> • PCR (blood)
Germany	<ul style="list-style-type: none"> • Combination of microscopy blood smear and thick film Giemsa, serology and PCR
Netherlands	<ul style="list-style-type: none"> • Microscopy: blood smear and thick film Giemsa • Serology: IFA (<i>B. microti</i>) • PCR: blood (drawn during fever, experimental. Detecting <i>Babesia microti</i>, <i>Babesia divergens</i> and <i>Babesia venatorum</i>)(RIVM)
Norway	<ul style="list-style-type: none"> • Microscopy. PCR (for reseach purposes). (Serology not available in public labs. Samples sent abroad if needed)
Sweden	<ul style="list-style-type: none"> • <i>B. microti/divergens</i>: Serology (IFA) (through the Public Health Agency) • Microscopy • PCR
Scotland (UK)	<ul style="list-style-type: none"> • Scotland: Microscopy from blood film in haematology laboratory can be requested. PCR experimental • England (London School of hygiene & Tropical Medicine): Serology (IFA)

Recommendations

Keep the possibility of babesiosis in mind in immunosuppressed patients with fever. Minimum testing should include microscopy. Use of both serology and PCR is recommended.

(Bartonellosis)

Bartonellosis is primarily a zoonotic cat's disease. Several different Bartonella bacteria can cause disease in humans. The microbe has been detected in ticks in Europe, but transmission of infection to humans by tick bites has not been demonstrated.

Therefore, routine testing for this pathogen after tick bites is not recommended, and further description is omitted from this document.

(Tularaemia)

The risk of getting tularaemia infection after tick bites in the North Sea Region is extremely low. Transmission of the causative agent, *Francisella tularensis*, from ticks to humans is rare, but possible (53, 54, 60).

Therefore, routine testing for this pathogen after tick bites is not recommended, and further description is omitted from this document.

Diagnosics. Summary table

Country	Borreliosis	Tick-borne encephalitis	Other tick-borne diseases
Belgium	EM: Clinical presentation, no serology NB: CSF with pleocytosis and intrathecal <i>Borrelia</i> specific IgG/IgM antibody index.	Serology; ELISA. Neutralisation test on equivocal and positive results	PCR, microscopy, serology (IFA)
Denmark	EM: Clinical presentation, no serology NB: CSF with pleocytosis and intrathecal <i>Borrelia</i> specific IgM/IgG antibody index CXCL13 in CSF	Real time TBE PCR in CSF and serum/urine Specific TBE IgG/IgM antibodies in CSF and serum (ELISA) Antibody titer in serum repeated to observe kinetics	PCR, microscopy, serology
Germany	EM: Clinical presentation, no serology NB: CSF with pleocytosis and Intrathecal <i>Borrelia</i> specific IgM/IgG antibody production; CXCL13 experimental	Clinical symptoms Serology; IgM/IgG in serum and intrathecal	PCR, microscopy, serology
Netherlands	EM: Clinical presentation, no serology NB: CSF with pleocytosis and intrathecal <i>Borrelia</i> specific IgM/IgG antibody index CXCL13 in CSF	Serology: ELISA RT-PCR: blood (drawn during fever), CSF	PCR, microscopy, serology
Norway	EM: Clinical presentation, no serology Serology: IgG and IgM ELISA. Immunoblot for possible false positive NB: CSF with pleocytosis and Intrathecal <i>Borrelia</i> specific IgM/IgG antibody index CXCL13 in CSF	Serum: PCR early, IgM, IgG CSF: PCR, IgM, IgG	PCR, microscopy (Serology not available in public labs)
Sweden	EM: Clinical presentation, no serology NB: CSF with pleocytosis and intrathecal <i>Borrelia</i> specific IgM/IgG antibody index, CXCL13 in CSF may be used as a complement PCR may be used as a complement to serology in suspected cases of borrelia arthritis, ACA and sometimes also in early NB	Detection of TBE-specific IgM in serum or significant elevation of IgG in paired serum samples by ELISA. IgM reactivities are recommended to be confirmed by a second, independent test Simultaneous CSF and serum antibody detection in previously vaccinated, IgM detection in CSF by a rapid test (immunochromatography) has been shown to be highly sensitive and specific PCR in CSF, serum, urine, available at some laboratories	PCR, microscopy, serology
Scotland (UK)	EM: Clinical presentation, no serology. NB: CSF with pleocytosis and intrathecal <i>Borrelia</i> specific IgG antibody index (CXCL13 in CSF may be complementary)	Not available in Scotland. England (RIPL): PCR and serology (serum and CSF)	PCR, microscopy, serology

Non-validated tests

Non-validated tests should not be used in diagnostic processes for tick-borne diseases. However, there are examples that such tests are used. This includes assays such as lymphocyte transformation test (LTT) and CD57⁺ cells (67, 78).

Concluding remarks – diagnostics

Feedback to the report-draft of January 12th 2022:

From stakeholders and at the NorthTick recommendations meeting June 15th 2022, at Fevik, Norway: Some patient organisations comment that the diagnostics of TBDs have generally become quite good. And that it is especially pleasing that work is done on developing an antibody test for Neoehrlichia, which is very much welcomed.

However, this recommendations document may have focused too much on over diagnosis, and not sufficiently on costs of under-diagnosing of tick-borne diseases. And the document is not always clear as to what serology is used i.e. ELISA, IFA etc.

These transnational processes have identified similarities, differences and gaps in testing for tick-borne diseases that needs to be addressed. Areas where better consistency is required are identified.

Treatment

Special recommendations may be given for children, in cases of pregnancy, or allergy. Prophylactic use of antibiotics after tick-bites is not recommended.

Erythema migrans

Penicillin is the first choice for treatment of EM in the Scandinavian countries (Sweden, Norway and Denmark), while doxycycline is the first choice in the other countries. A recent trial of phenoxymethylpenicillin versus amoxicillin and doxycycline for EM in Norway, gave equal outcomes regarding time-span for the EM rash to vanish, and there were no long-term complaints in either of the groups (17).

Some patients request extended or repeated courses of antibiotic therapy, after treatment for EM. There are very few documented treatment failures after EM. However, one recently published study showed an association with persistent symptoms at 12 months of follow-up in persons treated for EM, compared to reference cohorts (73). Resistance to antibiotics is not experienced as a problem in clinical practice. *B burgdorferi* does have natural or intrinsic resistance to some antibiotics, e.g. aminoglycosides. A more detailed discussion of this is given by Bamm et al (79).

Recurrences of erythema migrans are not uncommon. Studies have shown that a second episode of borreliosis is rarely due to a relapse, but instead due to a new infection (59).

Neuroborreliosis (NB)

Doxycycline is the first choice to treat early NB, except in the Netherlands where ceftriaxone is recommended first choice. Regarding late NB, and NB where an encephalitis or myelitis is expected, all countries except Sweden and Denmark and to some amount Norway treat with intravenous ceftriaxone, as stated in EFNS guidelines from 2010 (14). In Norway also intravenous penicillin is recommended as equal to ceftriaxone. When symptoms are less severe, intravenous treatment can be shifted to oral treatment (Norway).

Borrelia arthritis (BA) / Acrodermatitis chronica atrophicans (ACA)

In most of the North Sea Region countries, these clinical manifestations are treated with doxycycline. In Denmark, penicillin is recommended, with doxycycline as an alternative. Sometimes symptoms of borrelia arthritis can relapse, probably due to immunological processes in the affected joint (80).

Borrelia carditis (BC)

Doxycycline is recommended in all the North Sea Region countries. In Denmark, intravenous ceftriaxone is recommended until resolution of the atrioventricular (AV) block. When the condition is severe and requires hospitalization, the Netherlands and the UK also recommend intravenous ceftriaxone. A temporary pacemaker can be necessary due to AV block.

Other tick-borne diseases

Most countries treat other tick-borne diseases with doxycycline, except for babesiosis, which requires a different treatment. There is an overall agreement to treat babesiosis with a combination of azithromycin and atovaquone, or clindamycin and quinine.

All seven North Sea Region countries agree on supportive care for TBE and recommend TBE vaccination for people living or spending time outdoor in endemic areas. The TBE vaccine is not a treatment, and there is no general "tick vaccine" against the tick, or against other tick-borne diseases than TBE, although people often refer to TBE vaccine as a "tick vaccine". Until now there are just case-descriptions on experimental use of immune modulating therapy for severe TBE cases, none from North Sea Region countries.

Table 10: Treatment. Summary table

Country	Borreliosis	Tick-borne encephalitis	Other tick-borne diseases
Belgium	<p>EM: Doxycycline 100mg b.i.d. 10 days ("bis in die" = twice a day)</p> <p>NB:</p> <ul style="list-style-type: none"> •Early: Doxycycline 100mg b.i.d. 14 days •Late: Ceftriaxone 2g q.d. 4 weeks <p>ACA: Doxycycline 100mg b.i.d. 21-28 days</p> <p>BA: Doxycycline 100mg b.i.d. 28 days</p> <p>BC: Doxycycline 100mg b.i.d. 21 days</p>	Supportive care	<p>Anaplasmosis: Doxycycline 100mg b.i.d. 7 to 14 days</p> <p>Rickettsiosis: Doxycycline 100mg b.i.d. 7 days or until 2-3 days after disappearance fever</p> <p>Tularaemia: mild: ciprofloxacin (2x 500) or Doxy (2x100), 7-10 days.</p> <p>Severe: gentamicin IV</p> <p>Meningitis: gentamicine + Doxycycline</p>
Denmark	<p>EM: Penicillin V 1.5 MIE t.i.d. for 10 days</p> <p>NB:</p> <ul style="list-style-type: none"> •Early: Doxycycline 200 mg q.d. 1st day followed by 100 mg b.i.d. for 14 days •Late: Doxycycline 200 mg q.d. 1st day followed by 100 mg b.i.d. for 14-21 days <p>ACA: Penicillin V 1.5 MIE t.i.d. or doxycycline 100 mg b.i.d. for 21 days</p> <p>BA: Penicillin V 1.5 MIE t.i.d. or doxycycline 100 mg b.i.d. for 21 days</p> <p>BC: Ceftriaxone 2 g q.d. IV until resolution of AV block followed by doxycycline 100 mg b.i.d. for 14 days</p>	Supportive care	<ul style="list-style-type: none"> •Rickettsia spp.: Doxycycline 100 mg b.i.d. for 7-14 days •Tularaemia: Ciprofloxacin 750 mg b.i.d. or Doxycycline 100 mg b.i.d. for 14-21 days •Bartonella henselae: Azithromycin 500 mg on day 1, followed by 250 mg q.d. for 4 days •Babesiosis: Combination of quinine and clindamycin or atovaquone and azithromycin •<i>Anaplasma phagocytophilum</i>: Doxycycline 100 mg b.i.d. for 7-10 days •<i>Neoehrlichia mikurensis</i>: Doxycycline 100 mg b.i.d. for 3 weeks
Germany	<p>EM: Doxycycline 200 mg once or 100 mg b.i.d. 10-14 days</p> <p>Multiple EM: Doxycycline 200 mg once or 100 mg b.i.d. 21 days</p> <p>NB:</p> <ul style="list-style-type: none"> •Early: Doxycycline 200 mg once or 100mg b.i.d. 14 days <p>Late: Ceftriaxone 2g q.d. 2-3 week</p> <p>BC: Doxycycline 200 mg once or 100 mg b.i.d. 21 days</p> <p>ACA: Doxycycline 200 mg once or 100 mg b.i.d. 30 days</p> <p>BA: Doxycycline 200 mg once or 100 mg b.i.d. 30 days LC:</p>	Supportive care	<p>Anaplasmosis, Doxycycline 200 mg once or 100 mg b.i.d. 10-14 days</p> <ul style="list-style-type: none"> •Neoehrlichiosis unclear (doxycycline 200 mg) •Rickettsia spp. Doxycycline 200 mg for 14 days. •Babesiosis azithromycin and atovaquone/quinine and clindamycin for 7-10 days. •Tularaemia: Preferred therapy: Mild course: Ciprofloxacin 500mg PO 2x daily for 10-14 days; Severe course/hospitalisation:- Gentamicin 1x 5mg/kg IV plus ciprofloxacin 2x 500mg PO or 2x 400mg IV for 10-14 days Alternative therapy:- Doxycycline 100mg PO 2x d. for 14-21 days, or - Chloramphenicol 15 mg/kg IV 4x d. for 14-21 days

Netherlands	<p>EM: Doxycycline 100 mg b.i.d. 10 days</p> <p>NB:</p> <ul style="list-style-type: none"> •Early: Ceftriaxone IV 2g q.d. 14 days •Late: Ceftriaxone IV 2g q.d. 30 days <p>ACA: Doxycycline 100 mg b.i.d. 30 days</p> <p>BA: Doxycycline 100 mg b.i.d. 30 days</p> <p>BC: Ceftriaxone IV 2g q.d. 14 days or Doxycycline 100 mg b.i.d 21 days</p> <p>Multiple EM: Doxycycline 100 mg b.i.d 21 days</p>	Supportive care	<ul style="list-style-type: none"> •Anaplasmosis and ehrlichiosis Doxycycline •Babesiosis Combination of quinine and clindamycin or atovaquone and azithromycin •Rickettsiosis doxycycline 100mg x 2 for 7 days.
Norway	<p>EM: Penicillin 1g x 4 for 14 days</p> <p>NB:</p> <ul style="list-style-type: none"> •Early: Doxycycline 100mg b.i.d. 14 days •Late: Ceftriaxone <p>ACA: Doxycycline 100 mg b.i.d. 21 days</p> <p>BA: Doxycycline 100 mg b.i.d. 21 days</p> <p>BC: Doxycycline 100 mg b.i.d. 21 days</p>	Supportive care	<ul style="list-style-type: none"> •Babesiosis azithromycin and atovaquone/quinine and clindamycin for 7-10 days. •Other TBDs Doxycycline for 14 days
Sweden	<p>EM: Penicillin 1g t.i.d. 10 days</p> <p>NB:</p> <ul style="list-style-type: none"> •Early: Doxycycline 100 mg b.i.d. 14 days <p>ACA: Doxycycline 100 mg b.i.d 21 days</p> <p>BA: Doxycycline 100 mg b.i.d 21 days</p> <p>BC: Doxycycline 100 mg b.i.d 21 days</p>	Supportive care	<ul style="list-style-type: none"> •Babesiosis azithromycin 500 mg x 1 day 1, then 250 mg x 1 for 7-10 days together with atovaquone 750 mg x 2. Alternative: clindamycin 300-600 mg x 3 together with quinine 500 mg x 3 for 7-10 days •Other TBDs doxycycline 100 mg x 2 for 14 days.
Scotland (UK)	<p>EM: Doxycycline 100mg b.i.d. for 21 days (NICE 2018)</p> <p>NB affecting the cranial nerves and peripheral nervous system (most cases of NB): Doxycycline 100mg b.i.d. for 21 days, with Amoxicillin 1g t.i.d. for 21 days as first alternative.</p> <p>Whereas NB affecting the CNS: Ceftriaxone 2g IV b.i.d. for 21 days, with Doxycycline 200mg b.i.d. 21 days as first alternative.</p> <p>ACA: Doxycycline 100mg b.i.d. for 28 days</p> <p>BA: Doxycycline 100mg b.i.d. for 28 days</p> <p>BC: Doxycycline 100mg b.i.d. for 21 days if stable, ceftriaxone IV 2g q.d. for 21 days if unstable</p>	Supportive care	<p>Anaplasma: doxycycline 100mg twice a day for 10 days.</p> <p>B miyamotoi: Doxycycline 100mg twice daily for 14 days.</p> <p>Babesiosis: atovaquone and azithromycin OR clindamycin and quinine for 7-10 days.</p> <p>Rickettsiosis doxycycline for 7 days or until at least 3 days after fever resolved.</p> <p>Other TBD are managed by infectious diseases specialists</p>

Non-validated therapeutic measures are not recommended to treat tick-borne diseases. This includes long and repeated use of different antibiotic combinations, and disulfiram (44, 68, 69).

Discussion

Overall, recommendations for diagnostics and treatment of TBD in the North Sea Region are comparable and alike. However, there are some differences between the countries in choice and duration of antibiotics, and in mode of deliverance - oral or intravenously. Doctors can tell the patients that such differences in the treatment regimens are only “minor” – but some patients may get worried, confused and not convinced about the choice of treatment for their illness.

The treatment differences are probably based on different therapy traditions in each country, more than on research-based knowledge. With mounting evidence, this may change. In a European prospective, double blind study of adults with early NB, oral doxycycline was found to be as effective as ceftriaxone (50). Based on this study, various treatment guidelines now consider doxycycline as a reasonable first choice for NB. A randomized study comparing two versus six weeks of doxycycline for patients with NB is performed (51). No clinical benefit of a longer duration is identified (76).

While no studies have assessed the optimal duration of antibiotic therapy in borreliosis, the slow clinical resolution and long-term neurologic sequelae that may occur in some cases of NB, have led some clinicians to extend the duration of treatment up to 28 days. *Borrelia encephalomyelitis*, involving the brain parenchyma as evidenced by focal neurologic defects or magnetic resonance imaging findings, is extremely rare (74), and is typically treated with two to four weeks of intravenous ceftriaxone.

Regarding good antibiotic stewardship and avoiding development of antibiotic resistance, narrow spectrum antibiotics are preferred instead of broad-spectrum antibiotics. The duration of treatment should aim to be knowledge and research based.

“Antibiotics should be thought of like oil, a non-renewable resource to be carefully husbanded. What we use now cannot be used some time in the future.” (52).

Recommendations

The treatment regimens need to be aligned based on mounting research and evidence.

The use of narrow spectrum antibiotics are preferred.

Duration of antibiotic treatment needs to be evidence-based.

If there is an EM, with no additional symptoms and findings, the EM can be treated with penicillin or doxycycline for 10 days.

Intravenous treatment of borreliosis can be restricted to late diagnosed borreliosis with a duration of illness of more than 6 months, and considered in patients who have parenchymatous infections (encephalitis/ vasculitis/ myelitis).

After the first doses of ceftriaxone, a switch to oral treatment can be considered if the clinical situation improves.

Treatment durations of more than 3-4 weeks should not be used.

Feedback to the report-draft of January 12th 2022:

From stakeholders and at the NorthTick recommendations meeting June 15th 2022, at Fevik, Norway: Persons with residual symptoms after treatment should be followed closely, is a key message from the patient organisations.

There is high agreement within treatment guidelines for TBD in the seven North Sea Region countries. However, some differences in treatment guidelines can cause uncertainty for patients, especially for those with residual symptoms after completed treatment.

Inform the patient about choice of therapy, guide the patient to evidence-based information.

Systematic follow-up is important. Deal with residual symptoms, and rule out other disease manifestations.

Rehabilitation and follow-up

There are currently no systematic, national recommendations on rehabilitation and follow-up of persons with long-term symptoms after tick-borne or suspected tick-borne diseases in any of the countries within the North Sea Region.

Many countries have rehabilitation centres for other conditions with symptoms that might resemble those in long-time complaints after TBD; such as Myalgic Encephalopathy (ME) and Chronic Fatigue Syndrome (CFS). In most North Sea Region countries, follow-up and rehabilitation are scheduled by the specific hospital departments; e.g. infectious diseases, neurological or paediatric, based on individual assessments. The second opinion clinics sometimes provide rehabilitation recommendations (such as in Odense – Denmark, and in Amsterdam – the Netherlands).

It is recommendable to offer persons that have had NB or *Borrelia* arthritis a check-up one, three and possibly six months after treatment. This may identify residual symptoms to be intervened on, that may reduce long-term health problems. A re-evaluation of the primary diagnosis and treatment is important for people with persistent symptoms. Differential diagnoses must be considered. Further specialist assessments should be used when needed. Regardless of the final diagnosis and treatment, rehabilitation should be considered. Reports and data from second opinion clinics in the Netherlands, Denmark and Sweden tell us that it is very important to do a careful differential diagnostic work-up in persons who have long-term complaints that they associate with tick-borne diseases. More than one third of them have other diseases that may need further diagnostics and other treatment than antibiotics (32, 55, 65).

Status in the North Sea Region

Belgium

There is no organized follow-up of patients with tick-borne diseases, nor specific guidelines. Care is based on individual assessments.

Denmark

Follow-up regimens are not unified between Danish regions or hospitals.

Two national centres for vector-borne/tick-borne infections have established a systematic follow-up algorithm for patients with neuroborreliosis (NB). Furthermore, the units provide tele advice for doctors. They do comprehensive diagnostic work-ups.

Rigshospitalet:

- Assess treatment response 3 months after antibiotic therapy in patients diagnosed with borreliosis.
- Follow-up of NB patients after 1, 3 and 6 months.
- Sequelae after NB and TBE: same rehabilitation as for other infections in the central nervous system.

Centre for Complex Symptoms which is recently established, has a team of specialists. The focus is on rehabilitation and education of patients to move from seeking new investigation modalities, to maintenance of social relations and mental health. Some patients with borreliosis associated complaints - without any other evident somatic cause – and with no response to antibiotic therapy, can be referred for rehabilitation.

Odense: Follow-up of NB patients after 1, 3, 6 and 12 months. Follow-up includes regular cognitive testing and relevant rehabilitation. Participation of family/relatives is welcomed.

Germany

No specific rehabilitation for tick-borne diseases.

Tick-borne encephalitis follow-up and rehabilitation on individual basis concerning neurological symptoms according to affected organs, severity of symptoms and duration of symptoms. Rarely, and only on individual basis, for psychiatric complaints. No social rehabilitation except legal sick note for acute symptomatic TBE.

A national Borrelia league and local borrelia self-support groups exists. They focus on borrelioses, more rarely on TBE, but there is increasing interest also on so-called co-infections like babesiosis, borna-virus, anaplasmosis, ehrlichiosis, bartonellosis, chlamydia, yersinia or rickettsioses. Mainly based on non-scientific and non-professional ideas.

The Netherlands

No specific rehabilitation for tick-borne diseases.

Generally accepted policy:

- Assess antibiotic treatment success - 2-3 months after treatment in each patient with borreliosis
- Discuss with patient with chronic borreliosis associated complaints - without any other evident somatic cause – but with (serological) evidence of (prior) *B. burgdorferi* sl infection, the option of antibiotic treatment (i.e. 1 month doxycycline 100 mg b.i.d 30 days) and the (limited) expectations of such antibiotic treatment and possible side-effects (shared decision-making). In practice, this is usually done in expertise centres.
- When in the above-mentioned patients antibiotic is not opted for or unsuccessful, one should consider rehabilitation (with or without cognitive behavioural therapy), which is mostly locally organized (e.g. in physiotherapy, rehabilitation, psychology clinics).

Norway

No organized follow-up of patients with long-term symptoms after suspected TBD.

Each department do eventually follow-up (e.g. infectious diseases, paediatric, neurological).

The National Advisory Unit on Tick-borne Diseases is available on telephone / website / e-mail contact for doctors and patients every working day.

Other relevant rehabilitation centres: Centre for ME / Chronic Fatigue Syndrome in Oslo, National Advisory Unit for complex symptom disorders in Trondheim.

One institution at Sørlandet Hospital offers rehabilitation for chronic fatigue and pain (independent of cause).

Other rehabilitation centres for neurologic diagnoses.

Sweden

Lack national recommendations/standardization for follow-up and rehabilitation.

Follow-up after TBD primarily at the infectious diseases / paediatric / neurological department in each region.

Patients may be referred to Centre for Vector-Borne Infections, Uppsala Academic Hospital for further investigation.

Sequelae after neuroborreliosis and TBE: same rehabilitation as for other infections in the central nervous system.

ME/CFS (Myalgic Encephalopathy/Chronic Fatigue Syndrome) clinics in Stockholm, Gothenburg.

Scotland (United Kingdom)

There is no dedicated rehabilitation team for patients with borreliosis. Doctors can refer to local rehab team on ad hoc basis.

Long-term follow-up of infectious diseases on case-by-case basis in each health board in Scotland.

Patients can be referred to social service for assessments of daily living activities. Outpatient physiotherapy for graded exercise therapy.

Psychiatry services. Cognitive Behavioural Therapy (CBT).

Recommendations

Assess treatment success in, and offer follow-up for, persons treated for disseminated borreliosis. Provide a multiprofessional and specialised second opinion diagnostic in patients with long-term symptoms associated with tick-borne diseases and consider alternative diagnoses. Make sure patients in need have access to timely rehabilitation for their complaints, regardless of the final diagnosis.

Feedback to the report-draft of January 12th 2022:

From stakeholders and at the NorthTick recommendations meeting June 15th 2022, at Fevik, Norway:

The follow-up of persons with residual symptoms after TBDs has a big improvement potential is a key message from patient organisations.

Offer structured follow-up for persons treated for disseminated borreliosis.

Perform repeated assessments of persons with serious illness or residual symptoms/sequelae. It is crucial to offer a possibility for second opinion assessments.

Advice to doctors:

Perform comprehensive diagnostic assessments, give sound information and refer to quality assured websites.

Agree on follow-up and repeat assessments over time.

Do not give patients a sense of not being taken care of – left alone with their symptoms. Endure!

Advice on future activities

Involve stakeholders and patient organisations more in plans of future research activities on TBD.

A future project could be to build quality assured Tick web sites (in all languages) in the North Sea region, containing updated information on ticks and TBD for the public and health professionals.

Harmonise test-regimes for TBD in Europe, with recommendations as to which perform best.

Build competence networks for tests concerning rare tick-borne infections.

Build joint TBD biobanks.

Writing process of this report

After presentations and discussions, an elected writing group started working on a first draft, that comprised; Randi Eikeland; Background. Anne-Mette Lebech; Clinical practice in the North Sea Region. Chin Lim; Diagnostic pathways in NSR. Rosa Maja Møhring Gynthersen; Follow-up and rehabilitation.

Later versions of the draft has included input from stakeholders, the public and patient organisations.

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References

1. [NorthTick, Interreg VB North Sea Region Programme](#) Accessed June 24th 2021
2. Aavitsland P. En epidemi av borreliose? NRK Ytring 10.05.2013. https://www.nrk.no/ytring/en-epidemi-av-borreliose_-1.11021298 Accessed 25.2.2021.
3. Eliassen KE, Lindbæk M, Noraas S et al. Ensidig og feilaktig om flått. Dagbladet 25.10.2012. <https://www.dagbladet.no/kultur/ensidig-og-feilaktig-om-flaringtt/63241782> Accessed 25.2.2021.
4. The International Lyme and Associated Diseases Society (ILADS). Controversies & Challenges in Treating Lyme and Other Tickborne Diseases. <https://www.ilads.org/research-literature/controversies-challenges/> Accessed 25.2.2021.
5. Nordic consensus on the assessment and follow-up of persons with long-term ailments after suspected tick-borne diseases Oslo: The Norwegian Directorate of Health, 2020. https://www.helsedirektoratet.no/rapporter/nordisk-konsensus-om-utredning-og-oppfolging-av-personer-med-langvarige-plager-ved-mistenkte-flattbarne-sykdommer/pdf-versjon-av-rapporten/Report_Nordic_consensus_engelsk.pdf/_attachment/inline/6679a92c-c1d4-4d82-bba0-3e1b62706c64:6dae81041fd076a3d2eb76547843b98104237c2a/Report_Nordic_consensus_engelsk.pdf Accessed 25.2.2021
6. ArminLabs – Diagnosing tick-borne diseases. <https://arminlabs.com/en> Accessed 25.2.2021.
7. Laboratories RED. Phelix Phage borrelia test. <https://redlabs.be/> Accessed 25.2.2021.
8. Aase A, Hajdusek O, Øines Ø et al. Validate or falsify: Lessons learned from a microscopy method claimed to be useful for detecting Borrelia and Babesia organisms in human blood. *Infect Dis (Lon)* 2016; 48: 411–9.
9. Tveten Y, Noraas S, Aase A. Cellulære borreliatester. *Tidsskr Nor Legeforen* 2014; 134: 146–7.
10. Ulvestad E. Borreliosestriden. *Tidsskr Nor Legeforen* 2013; 133: 2234. [PubMed][CrossRef]
11. Harbo S, Blystad H, Nilsen S et al. Diagnostikk og behandling av Lyme borreliose – Rapport til Helsedirektoratet fra arbeidsgruppen. Oslo: Helsedirektoratet, 2009. https://www.helsedirektoratet.no/rapporter/rapport-om-diagnostisering-og-behandling-av-lyme-borrelioseflattsykdom/Rapport%20om%20diagnostisering%20og%20behandling%20av%20lyme%20borreliose%20fl%C3%A5ttsykdom.pdf/_attachment/inline/77022134-ede7-4157-85aa-48908d19c036:4a114c13a1a314fb40e579b51581a60602205b61/Rapport%20om%20diagnostisering%20og%20behandling%20av%20lyme%20borreliose%20fl%C3%A5ttsykdom.pdf Accessed 25.2.2021.
12. Reiso H, Kerlefsen Y, Aase A, Aaberge IS, Eliassen KE, Eikeland R. What should be done in cases of suspected tick-borne disease? *Tidsskr nor legeförening Tidsskr Nor Legeforen* 2021 doi: 10.4045/tidsskr.20.1006 <https://tidsskriftet.no/en/2021/05/kronikk/what-should-be-done-cases-suspected-tick-borne-disease>
13. Herwaldt B et al A fatal case of babesiosis in Missouri: identification of another piroplasm that infects humans. *Ann Intern Med.* 1996; 124(7):643).
14. Mygland A, Ljøstad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *European journal of neurology.* 2010;17(1):8-16, e1-4. <https://pubmed.ncbi.nlm.nih.gov/19930447/>
15. National Institute for Health and Care Excellence (NICE). Lyme disease NICE guidelines, 2018 <https://www.nice.org.uk/guidance/ng95/resources/lyme-disease-pdf-1837756839877> (Read on June 10, 2020)
16. Nemetha J, Bernasconi E, Heiningerc U et al. Update of the Swiss guidelines on post-treatment Lyme disease syndrome. *Swiss Med Wkly* 2016; 146. doi: 10.4414/smw.2016.14353.
17. Eliassen KE, Reiso H, Berild D, Lindbæk M. Comparison of phenoxymethylpenicillin, amoxicillin, and doxycycline for erythema migrans in general practice. A randomized controlled trial with a 1-year follow-up. *Clin Microbiol Infect.* 2018 Dec;24(12):1290-1296. doi: 10.1016/j.cmi.2018.02.028. Epub 2018 Mar 2. PMID: 29505880.
18. Franc Strle, Jeffrey A. Nelson, Eva Ruzic-Sabljić, Joze Cimperman, Vera Maraspin, Stanka Lotric-Furlan, Yu Cheng, Maria M. Picken, Gordon M. Trenholme and Roger N. Picken. European Lyme Borreliosis: 231 Culture-Confirmed Cases Involving Patients with Erythema Migrans. *Clinical Infectious Diseases.* Vol. 23, No. 1 (Jul., 1996), pp. 61-65 (5 pages)

19. Dessau RB, van Dam AP, Fingerle V, Gray J, Hovius JW, Hunfeld KP, Jaulhac B, Kahl O, Kristoferitsch W, Lindgren PE, Markowicz M, Mavin S, Ornstein K, Rupprecht T, Stanek G, Strle F. To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis: a position paper of ESGBOR, the ESCMID study group for Lyme borreliosis. *Clin Microbiol Infect.* 2018 Feb;24(2):118-124. doi: 10.1016/j.cmi.2017.08.025. Epub 2017 Sep 5. PMID: 28887186.
20. Hillerdal H, Henningsson AJ. "Serodiagnosis of Lyme borreliosis-is IgM in serum more harmful than helpful?" 2021; *Eur J Clin Microbiol Infect Dis.*
21. Diagnosis and treatment of Lyme disease – Report to the Norwegian Directorate of Health from the working group, Norwegian Directorate of Health 2009. https://www.helsedirektoratet.no/rapporter/rapport-om-diagnostisering-og-behandling-av-lyme-borreliose-flattsykdom/Rapport%20om%20diagnostisering%20og%20behandling%20av%20lyme%20borreliose%20fl%C3%A5ttsykdom.pdf/_attachment/inline/77022134-ede7-4157-85aa-48908d19c036:4a114c13a1a314fb40e579b51581a60602205b61/Rapport%20om%20diagnostisering%20og%20behandling%20av%20lyme%20borreliose%20fl%C3%A5ttsykdom.pdf (Read on June 10, 2020)
22. Laboratory diagnostics in Lyme disease, Norwegian National Institute of Public Health 2011. <https://www.fhi.no/globalassets/dokumenterfiler/tema/strategimoter/strategimote-3.-november-2011-laboratoriediagnostikk-ved-borreliose.pdf.pdf> (Read on June 10, 2020)
23. Treatment time for Lyme disease infection, SBU, Sweden, 2013. <https://www.sbu.se/sv/publikationer/SBU-utvararderar/behandling-med-antibiotika-for-patienter-med-borreliosa/> (Read June 10, 2020)
24. Laboratory diagnostics for tick-borne infections: Systematic literature search with sorting, Norwegian National Institute of Public Health 2019. <https://www.fhi.no/publ/2019/laboratoriediagnostikk-ved-flattbarne-infeksjoner/> (Read June 10, 2020)
25. Guidelines TBD Denmark? Statens Serum Institut. Borreliose (borreliainfektion) <https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsleksikon/b/borreliose>
26. Guidelines TBD The Netherlands? Lyme onder de loep. Gezondheidsraad, 2013. <https://www.gezondheidsraad.nl/documenten/adviezen/2013/06/26/lyme-onder-de-loep>
27. Guidelines TBD Germany? Lyme-Borreliose, Das Robert Koch-Institut. https://www.rki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_LymeBorreliose.html
28. Guidelines TBD Belgium. Sciensano. Lyme disease. <https://www.sciensano.be/en/health-topics/lyme-disease>
29. Other guidelines TBD. Sweden. Laboratoriediagnostik av borreliainfektion. En översyn av europeiska rekommendationer och aktuell metodik. Smittskyddsinstitutet, 2013. <https://www.folkhalsomyndigheten.se/contentassets/eef7c263a25f4095907742d0bc03762e/laboratoriediagnostik-av-borreliainfektion-2013-101-28.pdf>
30. Other guidelines. Scotland <https://www.nhsinform.scot/illnesses-and-conditions/infections-and-poisoning/lyme-disease/>
31. van Oort BEH, Hovelsrud GK, Risvoll C, Mohr CW, Jore S. A Mini-Review of Ixodes Ticks Climate Sensitive Infection Dispersion Risk in the Nordic Region. *Int J Environ Res Public Health.* 2020 Jul 27;17(15):5387. doi: 10.3390/ijerph17155387. PMID: 32726948; PMCID: PMC7432026.
32. Gynthersen RMM, Tetens MM, Ørbæk M, Haahr R, Fana V, Hansen K, Mens H, Andersen ÅB, Lebech AM. Classification of patients referred under suspicion of tick-borne diseases, Copenhagen, Denmark. *Ticks Tick Borne Dis.* 2021 Jan;12(1):101591. doi: 10.1016/j.ttbdis.2020.101591. Epub 2020 Oct 9. PMID: 33126203.
33. Testing for "new" tick-borne diseases, at: <https://northsearegion.eu/northtick/news/testing-for-new-tick-borne-diseases/> may 2021.
34. Huppertz, H. I., P. Bartmann, U. Heininger, V. Fingerle, M. Kinet, R. Klein, G. C. Korenke and H. J. Nentwich (2012). "Rational diagnostic strategies for Lyme borreliosis in children and adolescents: recommendations by the Committee for Infectious Diseases and Vaccinations of the German Academy for Pediatrics and Adolescent Health." *Eur J Pediatr* 171(11): 1619-1624.
35. Fingerle, Eiffert et al. 2017, Fingerle, V., H. Eiffert, A. Gessner, U. B. Göbel, H. Hofmann, K. P. Hunfeld, A. Krause, H.-W. Pfister, U. Reischl, A. Sing, G. Stanek, B. Wilske and L. Zöller (2017). *MiQ12 Lyme-Borreliose.* München, Jena, Urban & Fischer.

36. Hofmann, H., V. Fingerle, K. P. Hunfeld, H. I. Huppertz, A. Krause, S. Rauer, B. Ruf and g. Consensus (2017). "Cutaneous Lyme borreliosis: Guideline of the German Dermatology Society." *Ger Med Sci* 15: Doc14.
37. Kaiser, R., J. J. Archelos-Garcia, H. I. Huppertz, W. Jilg, R. S. and M. Sturzenegger (2020). Frühsommer-Meningoenzephalitis (FSME), S1-Leitlinie, . Leitlinien für Diagnostik und Therapie in der Neurologie. Online: . in: Deutsche Gesellschaft für Neurologie (Hrsg.), www.dgn.org/leitlinien (abgerufen am 31.07.2020).
38. Rauer, S., S. Kastenbauer, H. Hofmann, V. Fingerle, H. I. Huppertz, K. P. Hunfeld, A. Krause, B. Ruf and R. Dersch (2020). "Guidelines for diagnosis and treatment in neurology - Lyme neuroborreliosis." *Ger Med Sci* 18: Doc03
39. Raffetin, A., A. Saunier, K. Bouiller, P. Caraux-Paz, C. Eldin, S. Gallien, R. Jouenne, A. Belkacem, J. Salomon, O. Patey, E. Talagrand-Reboul, B. Jaulhac and A. Grillon (2020). "Unconventional diagnostic tests for Lyme borreliosis: a systematic review." *Clin Microbiol Infect* 26(1): 51-59.
40. Strizova Z, Patek O, Vitova L, Horackova M, Bartunkova J. Internet-based self-diagnosis of Lyme disease caused death in a young woman with systemic lupus erythematosus. *external icon Joint Bone Spine*. 2019 Jan 17. pii: S1297-319X(19)30003-X.;
41. Marzec NS, Nelson C, Waldron PR, et al. Serious bacterial infections acquired during treatment of patients given a diagnosis of chronic Lyme disease - United States. *MMWR Morb Mortal Wkly Rep*. 2017 Jun 16;66(23):607-609.
42. Lantos PM, Shapiro ED, Auwaerter PG, Baker PJ, Halperin JJ, McSweegan E, Wormser GP. Unorthodox alternative therapies marketed to treat Lyme disease. *external icon Clin Infect Dis*. 2015 Jun 15;60(12):1776-82.
43. Patel R, Grogg KL, Edwards WD, Wright AJ, Schwenk NM. Death from inappropriate therapy for Lyme disease. *external icon Clin Infect Dis*. 2000;31(4):1107-9.
44. Frankl S, Hadar PN, Yakhkind A, Lang AE, Sandsmark DK. Devastating Neurological Injury as a Result of Treatment of "Chronic Lyme Disease". *Mayo Clin Proc*. 2021 Jul;96(7):2005-2007. doi: 10.1016/j.mayocp.2021.05.011. PMID: 34218872.
45. Gyllemark P, Wilhelmsson P, Elm C, Hoornstra D, Hovius JW, Johansson M, Tjernberg I, Lindgren PE, Henningson AJ, Sjöwall J. Are other tick-borne infections overlooked in patients investigated for Lyme neuroborreliosis? A large retrospective study from South-eastern Sweden. *Ticks Tick Borne Dis*. 2021 Sep;12(5):101759. doi: 10.1016/j.ttbdis.2021.101759. Epub 2021 Jun 4. PMID: 34161869
46. Leeflang MM, Ang CW, Berkhout J, Bijlmer HA, Van Bortel W, Brandenburg AH, Van Burgel ND, Van Dam AP, Dessau RB, Fingerle V, Hovius JW, Jaulhac B, Meijer B, Van Pelt W, Schellekens JF, Spijker R, Stelma FF, Stanek G, Verduyn-Lunel F, Zeller H, Sprong H. The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis. *BMC Infect Dis*. 2016 Mar 25;16:140. doi: 10.1186/s12879-016-1468-4. PMID: 27013465; PMCID: PMC4807538.
47. Baarsma ME, Schellekens J, Meijer BC, Brandenburg AH, Souilljee T, Hofhuis A, Hovius JW, van Dam AP. Diagnostic parameters of modified two-tier testing in European patients with early Lyme disease. *Eur J Clin Microbiol Infect Dis*. 2020 Nov;39(11):2143-2152. doi: 10.1007/s10096-020-03946-0. Epub 2020 Jul 6. PMID: 32632699; PMCID: PMC7561539.
48. Koetsveld J, Kolyasnikova NM, Wagemakers A, Toporkova MG, Sarksyas DS, Oei A, Platonov AE, Hovius JW. Development and optimization of an in vitro cultivation protocol allows for isolation of *Borrelia miyamotoi* from patients with hard tick-borne relapsing fever. *Clin Microbiol Infect*. 2017 Jul;23(7):480-484. doi: 10.1016/j.cmi.2017.01.009. Epub 2017 Jan 18. PMID: 28110053.
49. Telford SR, Goethert HK, Molloy PJ, Berardi V. Blood Smears Have Poor Sensitivity for Confirming *Borrelia miyamotoi* Disease. *J Clin Microbiol*. 2019 Feb 27;57(3):e01468-18. doi: 10.1128/JCM.01468-18. PMID: 30626663; PMCID: PMC6425185.
50. Ljøstad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, Mygland A. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. *Lancet Neurol*. 2008 Aug;7(8):690-5. doi: 10.1016/S1474-4422(08)70119-4. Epub 2008 Jun 21. Erratum in: *Lancet Neurol*. 2008 Aug;7(8):675. PMID: 18567539.

51. Solheim AM, Ljøstad U, Mygland Å. Six versus two weeks treatment with doxycycline in Lyme neuroborreliosis: the protocol of a multicentre, non-inferiority, double-blinded and randomised controlled trial. *BMJ Open*. 2019 Jun 14;9(6):e027083. doi: 10.1136/bmjopen-2018-027083. PMID: 31201188; PMCID: PMC6576128.
52. Del Mar C. Prescribing antibiotics in primary care. *BMJ*. 2007 Sep 1;335(7617):407-8. doi: 10.1136/bmj.39307.642963.80. PMID: 17762001; PMCID: PMC1962860.
53. Haulrig MB, Mathiasen G, Nielsen RM, Kromann CB, Krogfelt KA, Wiese L. Two cases of tick-borne transmitted tularemia on Southern Zealand, Denmark. *APMIS*. 2020 Jan;128(1):61-64. doi: 10.1111/apm.13008. PMID: 31691353.
54. Richard S, Oppliger A. Zoonotic occupational diseases in forestry workers - Lyme borreliosis, tularemia and leptospirosis in Europe. *Ann Agric Environ Med*. 2015;22(1):43-50. doi: 10.5604/12321966.1141368. PMID: 25780827.
55. Coumou J, Herkes EA, Brouwer MC, van de Beek D, Tas SW, Casteelen G, van Vugt M, Starink MV, de Vries HJ, de Wever B, Spanjaard L, Hovius JW. Ticking the right boxes: classification of patients suspected of Lyme borreliosis at an academic referral center in the Netherlands. *Clin Microbiol Infect*. 2015 Apr;21(4):368.e11-20. doi: 10.1016/j.cmi.2014.11.014. Epub 2014 Nov 22. PMID: 25658524.
56. https://www.euro.who.int/_data/assets/pdf_file/0008/246167/Fact-sheet-Lyme-borreliosis-Eng.pdf
57. https://www.euro.who.int/_data/assets/pdf_file/0010/246169/Fact-sheet-Tick-borne-encephalitis-Eng.pdf
58. <https://www.ecdc.europa.eu/en/all-topics-z/human-granulocytic-anaplasmosis/factsheet-human-granulocytic-anaplasmosis>
59. Nadelman RB, Hanincová K, Mukherjee P, Liveris D, Nowakowski J, McKenna D, Brisson D, Cooper D, Bittker S, Madison G, Holmgren D, Schwartz I, Wormser GP. Differentiation of reinfection from relapse in recurrent Lyme disease. *N Engl J Med*. 2012 Nov 15;367(20):1883-90. doi: 10.1056/NEJMoa1114362. PMID: 23150958; PMCID: PMC3526003.
60. Markowicz M, Schötta AM, Penatzer F, Matscheko C, Stanek G, Stockinger H, Riedler J. Isolation of *Francisella tularensis* from Skin Ulcer after a Tick Bite, Austria, 2020. *Microorganisms*. 2021 Jun 29;9(7):1407. doi: 10.3390/microorganisms9071407. PMID: 34209915; PMCID: PMC8304467.
61. Henningson Anna J., Aase Audun, Bavelaar Herjan, Flottorp Signe, Forsberg Pia, Kirkehei Ingvild, Lövmar Matilda, Nilsson Kenneth, Nyman Dag, Ornstein Katharina, Sjöwall Johanna, Skogman Barbro H., Tjernberg Ivar, Aaberge Ingeborg. Laboratory Methods for Detection of Infectious Agents and Serological Response in Humans With Tick-Borne Infections: A Systematic Review of Evaluations Based on Clinical Patient Samples. *Frontiers in Public Health*, 9, 2021, 1351. www.frontiersin.org/article/10.3389/fpubh.2021.580102 Doi 10.3389/fpubh.2021.580102
62. Portillo A, Santibáñez P, Palomar AM, Santibáñez S, Oteo JA. 'Candidatus *Neoehrlichia mikurensis*' in Europe. *New Microbes New Infect*. 2018 Jan 6;22:30-36. doi: 10.1016/j.nmni.2017.12.011. PMID: 29556406; PMCID: PMC5857181.
63. Welinder-Olsson C., Kjellin E., Vaht K., Jacobsson S., Wenneras C. First case of human 'Candidatus *Neoehrlichia mikurensis*' infection in a febrile patient with chronic lymphocytic leukemia. *J Clin Microbiol*. 2010;48:1956–1959.
64. <https://www.ecdc.europa.eu/en/all-topics-z/babesiosis/facts-about-babesiosis>
65. Kenneth Nilsson, Björn Olsen. <https://lakartidningen.se/klinik-och-vetenskap-1/nya-ron/2021/05/kronisk-borrelios-var-inte-unikt-kopplad-till-borreliainfektion/>
66. Sykes & Makiello. An estimate of Lyme borreliosis incidence in Western Europe. *Journal of Public Health* | Vol. 39, No. 1, pp. 74–81 | doi:10.1093
67. Raffetin A, Saunier A, Bouiller K, Caraux-Paz P, Eldin C, Gallien S, Jouenne R, Belkacem A, Salomon J, Patey O, Talagrand-Reboul E, Jaulhac B, Grillon A. Unconventional diagnostic tests for Lyme borreliosis: a systematic review. *Clin Microbiol Infect*. 2020 Jan;26(1):51-59. doi: 10.1016/j.cmi.2019.06.033. Epub 2019 Jul 12. PMID: 31306793
68. Berende A, ter Hofstede HJ, Vos FJ, van Middendorp H, Vogelaar ML, Tromp M, van den Hoogen FH, Donders AR, Evers AW, Kullberg BJ. Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease. *N Engl J Med*. 2016 Mar 31;374(13):1209-20. doi: 10.1056/NEJMoa1505425. PMID: 27028911.

69. Trautmann A, Gascan H, Ghozzi R. Potential Patient-Reported Toxicities With Disulfiram Treatment in Late Disseminated Lyme Disease. *Front Med (Lausanne)*. 2020 Apr 20;7:133. doi: 10.3389/fmed.2020.00133. PMID: 32373619; PMCID: PMC7184924.
70. Henningsson AJ, Asgeirsson H, Hammas B, Karlsson E, Parke Å, Hoornstra D, Wilhelmsson P, Hovius JW. Two cases of *Borrelia miyamotoi* meningitis, Sweden, 2018. *Emerg Infect Dis* 2019;25(10):1965-8.
71. Wass L, Grankvist A, Mattsson M, Gustafsson H, Krogfelt K, Olsen B, Nilsson K, Mårtensson A, Quarsten H, Henningsson AJ, Wennerås C. Serological reactivity to *Anaplasma phagocytophilum* in neoehrlichiosis patients. *Eur J Clin Microbiol Infect Dis* 2018;37(9):1673-8.
72. Höper L, Skoog E, Stenson M, Grankvist A, Wass L, Olsen B, Nilsson K, Mårtensson A, Söderlind J, Sakinis A, Wennerås C. Vasculitis due to *Candidatus Neoehrlichia mikurensis*: A Cohort Study of 40 Swedish Patients. *Clin Infect Dis*. 2021 Oct 5;73(7):e2372-e2378. doi: 10.1093/cid/ciaa1217. PMID: 32818961.
73. Vrijmoeth HD, Ursinus J, Harms MG, Zomer TP, Gauw SA, Tulen AD, Kremer K, Sprong H, Knoop H, Vermeeren YM, van Kooten B, Joosten LAB, Kullberg BJ, Hovius JWR, van den Wijngaard CC. Prevalence and determinants of persistent symptoms after treatment for Lyme borreliosis: study protocol for an observational, prospective cohort study (LymeProspect). *BMC Infect Dis*. 2019 Apr 15;19(1):324. doi: 10.1186/s12879-019-3949-8. PMID: 30987580; PMCID: PMC6466793.
74. Knudtzen FC, Eikeland R, Bremell D, Quist-Paulsen E, Johansen IS, Solheim AM, Skarphédinsson S. Lyme neuroborreliosis with encephalitis; a systematic literature review and a Scandinavian cohort study. *Clin Microbiol Infect*. 2021 Nov 9:S1198-743X(21)00628-5. doi: 10.1016/j.cmi.2021.11.001. Epub ahead of print. PMID: 34768019.
75. van Dop WA, Kersten MJ, de Wever B, Hovius JW. Seronegative lyme neuroborreliosis in a patient using rituximab. *BMJ Case Rep*. 2013 Feb 14;2013:bcr2012007627. doi: 10.1136/bcr-2012-007627. PMID: 23417373; PMCID: PMC3604215.
76. Solheim AM, Lorentzen ÅR, Dahlberg AO, Flemmen HØ, Brune S, Forselv KJN, Pripp AH, Bø MH, Eikeland R, Reiso H, Mygland Å, Ljøstad U. Six versus 2 weeks treatment with doxycycline in European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blinded, randomised and placebo-controlled trial. *J Neurol Neurosurg Psychiatry*. 2022 Jul 27;jnnp-2022-329724. doi: 10.1136/jnnp-2022-329724. Epub ahead of print. PMID: 35896378.
77. Ursinus J, Vrijmoeth HD, Harms MG, Tulen AD, Knoop H, Gauw SA, Zomer TP, Wong A, Friesema IHM, Vermeeren YM, Joosten LAB, Hovius JW, Kullberg BJ, van den Wijngaard CC. Prevalence of persistent symptoms after treatment for lyme borreliosis: A prospective observational cohort study. *Lancet Reg Health Eur*. 2021 May 27;6:100142. doi: 10.1016/j.lanepe.2021.100142. PMID: 34557833; PMCID: PMC8454881.
78. Baarsma ME, van de Schoor FR, Gauw SA, Vrijmoeth HD, Ursinus J, Goudriaan N, Popa CD, Ter Hofstede HJ, Leeflang MM, Kremer K, van den Wijngaard CC, Kullberg BJ, Joosten LA, Hovius JW. Diagnostic parameters of cellular tests for Lyme borreliosis in Europe (VICTORY study): a case-control study. *Lancet Infect Dis*. 2022 Sep;22(9):1388-1396. doi: 10.1016/S1473-3099(22)00205-5. Epub 2022 Jun 14. PMID: 35714662.
79. Bamm VV, Ko JT, Mainprize IL, Sanderson VP, Wills MKB. Lyme Disease Frontiers: Reconciling *Borrelia* Biology and Clinical Conundrums. *Pathogens*. 2019 Dec 16;8(4):299. doi: 10.3390/pathogens8040299. PMID: 31888245; PMCID: PMC6963551.
80. Arvikar SL, Crowley JT, Sulka KB, Steere AC. Autoimmune Arthritides, Rheumatoid Arthritis, Psoriatic Arthritis, or Peripheral Spondyloarthritis Following Lyme Disease. *Arthritis Rheumatol*. 2017 Jan;69(1):194-202. doi: 10.1002/art.39866. PMID: 27636905; PMCID: PMC5195856.

Surveillance sources

ECDC <https://www.ecdc.europa.eu/en/publications-data/tick-borne-encephalitis-annual-epidemiological-report-2016-2014-data>

Belgium

<https://epidemiologie.wiv-isp.be/ID/reports/Zoonoses%20et%20maladies%20vectorielles%202018.pdf>

https://organesdeconcertation.sante.belgique.be/sites/default/files/documents/gids_lyme_borreliose_fr_march2017.pdf

<https://pubmed.ncbi.nlm.nih.gov/31752967/>

Germany

TBE: <https://www.ecdc.europa.eu/en/publications-data/country-profile-germany-tick-borne-encephalitis-tbe>

The Netherlands

Lyme borreliosis: CBO richtlijn Lymeziekte, July 2013, <https://www.rivm.nl/documenten/cbo-richtlijn-lymeziekte-juli-2013>

TBEV: LCI richtlijn Tekenencefalitis, <https://lci.rivm.nl/richtlijnen/tekenencefalitis>

Anaplasma: LCI richtlijn Anaplasmosis en Ehrlichiose, <https://lci.rivm.nl/richtlijnen/anaplasmosis-en-ehrlichiose>

Babesia: LCI richtlijn Babesiosis, <https://lci.rivm.nl/richtlijnen/babesiosis>

Rickettsia: LCI richtlijn Vlektyfus, <https://lci.rivm.nl/richtlijnen/vlektyfus>

United Kingdom (Scotland)

<https://www.legislation.gov.uk/asp/2008/5/schedules/data.xht?view=snippet&wrap=true>

Norway

TBE: <https://www.ecdc.europa.eu/en/publications-data/country-profile-norway-tick-borne-encephalitis-tbe>

Lyme borreliosis: <http://www.msis.no/>

Sweden

Lyme neuroborreliosis: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6530252/>

TBE: <https://www.ecdc.europa.eu/en/publications-data/country-profile-sweden-tick-borne-encephalitis-tbe>

Denmark

Lyme neuroborreliosis:

<https://statistik.ssi.dk/sygdomsdata#!/?sygdomskode=NEBO&xaxis=Aar&show=Graph&datatype=Individual>

TBE: <https://www.ecdc.europa.eu/en/publications-data/country-profile-denmark-tick-borne-encephalitis-tbe>