Health Council of the Netherlands

A closer look at Lyme disease

Gezondheidsraad
Health Council of the Netherlands

To the President of the Dutch House of Representatives

Subject : presentation of advisory report *A closer look at Lyme disease*
Your reference : letter from the President of the Dutch House of Representatives April 27, 2011
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Dear President,

I hereby submit the advisory report entitled *A closer look at Lyme disease*. This report was drawn up by a Health Council committee specially appointed for the purpose. The purpose of this letter is to explain the background to the advisory report and to draw your attention to various findings of potential importance for the Dutch House of Representatives.

A wide-ranging advisory process

This advisory report is a very special one for the Health Council, as it is the first time that the Council has received a request that originated as a Citizens' Initiative. This was one of the reasons for specifically including patients' and physicians' perspectives in the advisory process. Focus group surveys were used to explore the experiences and visions of stakeholder groups in greater detail.

The Committee also asked the Dutch Cochrane Centre (DCC) to carry out a literature review to enable well-founded statements to be made about one of the most highly debated issues in Lyme disease: long-term antibiotic therapy for persistent symptoms and complaints.

This focus on the perspectives of those affected and contracting out the study to the DCC both took considerable time. By taking this approach, however, the Committee is now in a position to deliver a well-considered advisory report. This caution is essential, largely due to the uncertainty that occasionally plagues patients and physicians in the current situation. I agree with the approach taken by the Committee and I share its conclusions. The advisory

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report has been reviewed by the Standing Committee on Medicine and the Standing Committee on Infection and Immunity, two permanent Health Council advisory committees.

Main points of special interest

In most cases, Lyme disease is identified in good time and successfully treated. However, it is important to remember that both diagnostic laboratory tests for Lyme disease and treating its later stages still pose considerable difficulties. Other countries are faced with exactly the same issues.

The advisory report shows that current laboratory tests do not always provide an urgently needed answer, forcing patients to take repeated tests in several different laboratories. Accordingly, there is an urgent need for standardisation among these laboratories. In addition, there is often a lack of clarity concerning the procedures followed in non-accredited laboratories and the reliability of their results. At the same time, under current legislation, the Netherlands' Health Care Inspectorate lacks the means to effectively supervise these non-accredited laboratories. An extension of the legal instruments available to the Inspectorate in this area would be very welcome indeed.

At various points throughout the advisory report, the Committee alludes to the complex nature of Lyme disease and the uncertainty involved in diagnosis. This complexity and uncertainty give rise to considerable debate both in physicians' consulting rooms and in society at large. Finding common viewpoints is proving to be something of a challenge. While the resultant dynamism is quite understandable, it is ultimately not in the interests of patient care. The purpose of many of the Committee's recommendations is to clarify the situation. Accordingly, I very much hope that this advisory report will help physicians and patients to find common viewpoints on which to base appropriate treatment.

Yours sincerely,
(signed)
Professor W.A. van Gool,
President

A closer look at Lyme disease

to:

the President of the Dutch House of Representatives

No. 2013/12E, The Hague, June 26, 2013

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with health technology assessment.

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Executive summary

A complex picture

When diagnosed at an early stage, following a tick bite, Lyme disease responds well to treatment with antibiotics. However, the picture becomes more complex in patients whose symptoms are not particularly clear. The same is true of patients with later stage disease. Some individuals may experience persistent symptoms whose cause cannot clearly be linked to Lyme disease.

This is both stressful for patients and a real challenge for physicians. Within the profession itself, for example, there is disagreement concerning the best way to deal with persistent complaints. The matter is made even more complex by the vast amount of information available on the internet, which can vary enormously in terms of content and reliability. This can sometimes make it difficult to reach a common viewpoint.

This situation led the Dutch Association for Lyme Patients to submit a citizens' initiative to the Lower House of the Dutch Parliament. The Lower House then turned to the Health Council of the Netherlands. It asked the Council to review the level of knowledge, to identify any gaps in the relevant body of scientific knowledge, and to formulate recommendations.

The Council acted on these instructions, with a view to helping physicians and patients to reach common viewpoints. It enlisted a broad-based committee of experts, harnessed the best available knowledge, and used the experiences of all those involved.

Early-stage and late-stage Lyme disease

Borrelia, the bacterium that causes Lyme disease, is transmitted by ticks. There are a range of species of the bacterium, with different species (or combinations of species) occurring in different countries. Not every tick is infected, nor indeed does a bite from an infected tick inevitably result in Lyme disease. If ticks are removed quickly, this reduces the risk of infection.

However, if an infection does develop, then a range of visible effects can appear. Early localised Lyme disease is when the first, most characteristic, symptom appears. Known as erythema migrans (EM), this is usually a ring-shaped, red-coloured, spreading skin rash, also referred to as bullseye rash. The disease can then spread to the joints (Lyme arthritis) or to the nervous system (neuroborreliosis), and can run a severe course. This is referred to as early disseminated Lyme disease.

A diagnosis of acrodermatitis chronica atrophicans (or ACA) is indicative of late-stage Lyme disease. This is a dark red or purple discolouration of the skin, often appearing on the limbs. Neuroborreliosis, Lyme arthritis and Lyme carditis can also occur at this stage. Aside from the specific symptoms associated with these clinical pictures, complaints such as headaches, muscular pain and fatigue can also occur. The thorny issue here, however, is that the latter complaints are not restricted to Lyme disease alone.

It is not yet fully understood how the bacterium in question is able to give rise to these very different clinical pictures.

Making a diagnosis

A carefully compiled case history and a physical examination are essential elements in reaching a diagnosis of Lyme disease. In many cases, the “bullseye” is easily recognizable. However, erythema migrans can take other forms, and may not always be present, making it more difficult to reach a diagnosis.

Laboratory testing is often used in an attempt to resolve this issue. In the case of Lyme disease, however, the results of such tests can be difficult to interpret. The reasons for this are as follows. Firstly, the time at which the test takes place is of significance. The antibody test (the test most commonly used) initially produces a negative result, as it takes patients several weeks to develop antibodies. Secondly, tests that detect antibodies are unable to distinguish between an infection that is still active and one that has been effectively treated.

This is because antibodies remain in the blood for years, even after the bacteria have been eliminated from the body.

Furthermore, many different antibody test kits are in use, not all of which have been validated. These kits also differ in terms of the test procedures involved. In addition, many other types of methods are in use. As a result, contradictory test results may be obtained. Driven by the desire for a conclusive result, patients may take repeated tests in different laboratories, sometimes outside the Netherlands.

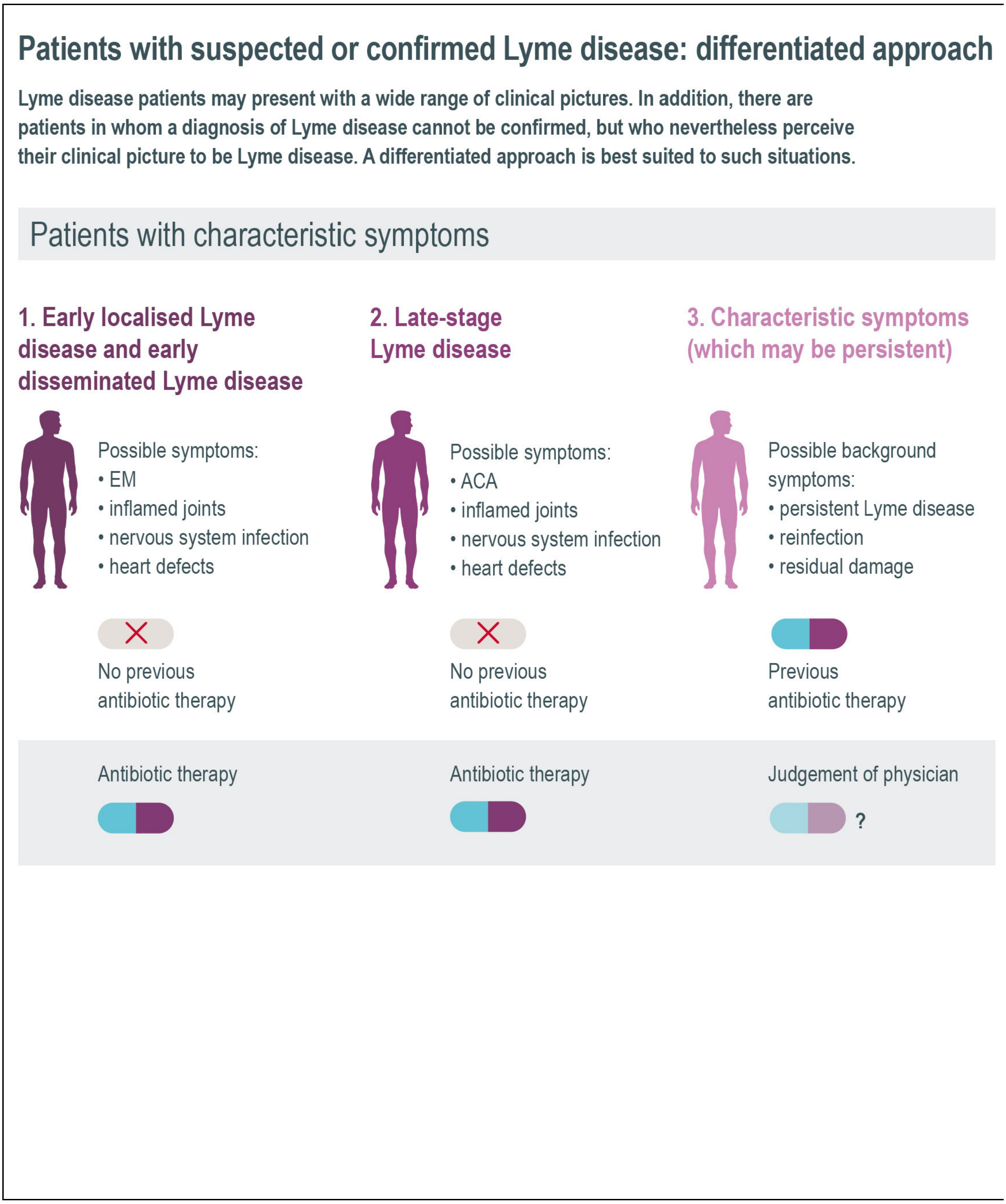
Therapy in a range of different situations

If Lyme disease has been diagnosed then antibiotic therapy is indicated, preferably as soon as possible. Most of these patients will make a full and complete recovery. Occasionally, however, such treatment is not fully effective, and patients continue to suffer from symptoms characteristic of Lyme disease. Another course of antibiotics is then indicated.

In some cases, there may also be residual damage that heals slowly, if at all. Alternatively, following their course of treatment, some patients may exhibit long-term complaints that are not typical of Lyme disease. The view that these complaints are caused by a persistent, active infection leads some physicians to prescribe long-term antibiotic therapy, although the effectiveness of this approach is by no means certain. A study carried out specifically for the purposes of this advisory report failed to find evidence that long-term antibiotic use has any beneficial effects. By the same token, however, it was unable to exclude the existence of such effects.

In this situation, and in the light of current knowledge, there is a need for clear policy. Different individuals exhibit widely varying stages of the disease on their first visit to a physician. Their symptoms and complaints will vary, as will their treatment history. In view of this, six distinct groups have been identified, each with its own recommended approach.

The most difficult aspect here is how to tackle long-term complaints that are not characteristic of Lyme disease, such as fatigue, headache and muscular pain (groups 4, 5 and 6). This poses a challenge to both patients and physicians. While antibodies to Lyme disease are present in groups 4 and 5, this does not necessarily mean that their persistent symptoms are actually due to this disease, even though that may be a possibility. Physicians can prescribe a course (or a further course) of antibiotics in such cases. Alternatively, they may decide to explore other treatment options.



Patients with suspected or confirmed Lyme disease: differentiated approach

Lyme disease patients may present with a wide range of clinical pictures. In addition, there are patients in whom a diagnosis of Lyme disease cannot be confirmed, but who nevertheless perceive their clinical picture to be Lyme disease. A differentiated approach is best suited to such situations.

Patients with characteristic symptoms

1. Early localised Lyme disease and early disseminated Lyme disease

Possible symptoms:
- EM
- inflamed joints
- nervous system infection
- heart defects

No previous antibiotic therapy

Antibiotic therapy

2. Late-stage Lyme disease

Possible symptoms:
- ACA
- inflamed joints
- nervous system infection
- heart defects

No previous antibiotic therapy

Antibiotic therapy

3. Characteristic symptoms (which may be persistent)

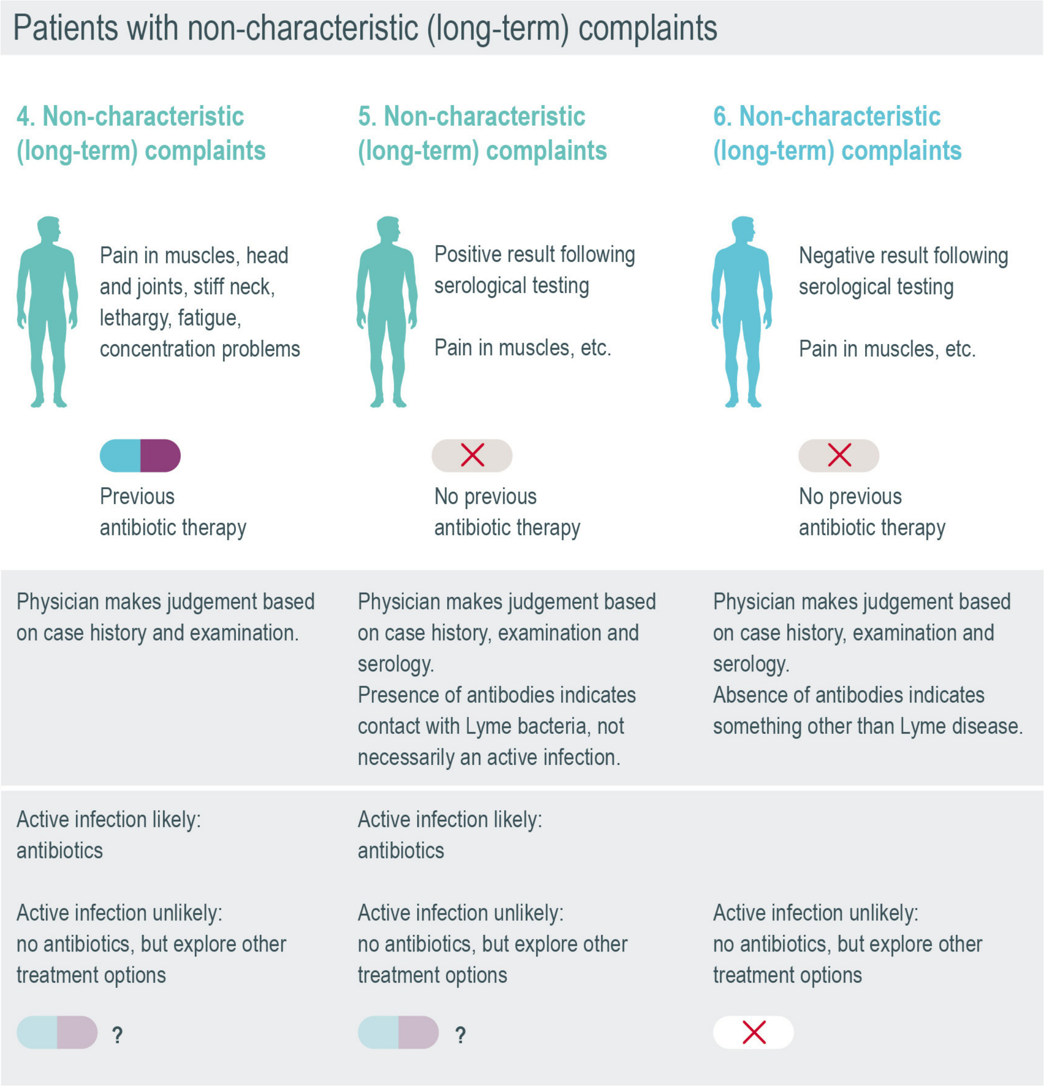
Possible background symptoms:
- persistent Lyme disease
- reinfection
- residual damage

Previous antibiotic therapy

Judgement of physician

Figure Patients with suspected or confirmed Lyme disease: diferentiated approach.

Group 6 contains patients in whom no antibodies can be detected. This means that their symptoms are probably due to something other than Lyme disease. In such cases, it makes little sense to prescribe antibiotics. Here too, alternative treatment perspectives should be offered.



Patients with non-characteristic (long-term) complaints

4. Non-characteristic (long-term) complaints	5. Non-characteristic (long-term) complaints	6. Non-characteristic (long-term) complaints
Pain in muscles, head and joints, stiff neck, lethargy, fatigue, concentration problems	Positive result following serological testing Pain in muscles, etc.	Negative result following serological testing Pain in muscles, etc.
💊 Previous antibiotic therapy	✗ No previous antibiotic therapy	✗ No previous antibiotic therapy
Physician makes judgement based on case history and examination.	Physician makes judgement based on case history, examination and serology. Presence of antibodies indicates contact with Lyme bacteria, not necessarily an active infection.	Physician makes judgement based on case history, examination and serology. Absence of antibodies indicates something other than Lyme disease.
Active infection likely: antibiotics	Active infection likely: antibiotics	
Active infection unlikely: no antibiotics, but explore other treatment options	Active infection unlikely: no antibiotics, but explore other treatment options	Active infection unlikely: no antibiotics, but explore other treatment options
💊 ?	💊 ?	✗

In this connection, it is important to adopt a comprehensive approach, with a focus on physical, psychological, and social factors. Cognitive behavioural therapy has been shown to be effective in the treatment of complaints that persist after treatment for disorders such as cancer. There have, as yet, been no studies into the effectiveness of courses of cognitive behavioural therapy specifically tailored to the context of Lyme disease.

Learning from experience

The Committee did not restrict its advisory process to the level of knowledge in this field, it also drew on people's real-life experiences. To this end, it held focus group meetings involving patients, physicians, and high-risk groups. The above-mentioned problems with diagnosis and treatment, which are discussed here from a scientific perspective, were echoed in everyday situations. Those concerned also expressed the view that there was a lack of knowledge about Lyme disease among physicians. In addition, both physicians and patients felt that their consulting room discussions were sometimes rather strained and awkward.

Strengthening common viewpoints

Lyme disease can pose difficult challenges, both for patients and physicians. In some cases the potential benefits of a course of antibiotics are not immediately apparent, nor has it been confirmed that the symptoms involved are actually due to Lyme disease. This uncertainty can undermine the relationship between patients and their physicians.

This underscores the importance of well-founded and widely accepted viewpoints. The Committee has made a number of recommendations to this end, one of which was that research should be carried out into improved test methods. It also recommended that such tests should routinely be carried out by accredited laboratories. The training (and continuing education) of physicians in the field of Lyme disease should be reviewed and improved where necessary. Studies involving patients with a confirmed diagnosis of Lyme disease could help to shed light on factors that influence the course of the disease.

Any meaningful discussion of the pros and cons of long-term antibiotic therapy will have to await the results of an on-going study into this issue. If the results provide sufficient useful information, then existing recommendations on antibiotic use can be reviewed. If not, then more research will be needed.

The recognition and treatment of Lyme disease could be improved by establishing a network of specialised treatment centres. Persistent complaints or residual damage require a broad-based approach. It is also important to keep an open mind with regard to all of the possible factors that might be involved. Cooperation between specialists can be helpful in this regard.

In addition, the government should provide the public with clear information about Lyme disease. After all, prevention is better than cure. Indeed, many fine initiatives have already been launched to this end.

Together with other recommended measures, these steps will be important in alleviating public uncertainty about the diagnosis and treatment of Lyme disease. This is in the interests of good patient care, including the care of those whose complaints do not appear to be linked to Lyme disease. It will also help physicians and patients to discuss appropriate treatment, based on common viewpoints.

Chapter 1

Introduction

1.1 Background to the advisory process

Lyme disease, an infectious bacterial disease transmitted to humans by ticks, has been a hot topic in recent years. The disease appears to be on the rise. GPs are registering increasing numbers of patients with tick bites and Lyme disease. The general public also has many questions, while various stories and theories about the disease (from a variety of sources) are circulating on the internet. This leads to confusion, both on the part of patients and physicians. Another debate is about whether there really is any such a thing as ‘chronic Lyme disease’. Do long-term complaints after treatment really indicate bacterial persistence?

The physicians involved have yet to take a clear stance in this debate. Indeed, some aspects of this debate concern issues within the medical profession itself. Some physicians are convinced that persistent complaints after treatment indicate persistence of the bacteria in question. As a result, they submit their patients to long-term antibiotic therapy, in some cases for several years. At the other end of the spectrum there are physicians who dismiss Lyme disease as an uncomplicated disease with a straightforward diagnosis and an excellent prognosis. These differing views hardly inspire confidence on the part of patients, who are unsure about what they should and should not believe. This debate is centred in the United States. The ferocity of the debate among some patients and physicians there has led to it being described as “Lyme Wars”. In the Netherlands, this is a controversial issue as well. This is reflected in part by the

Citizens' Initiative submitted to the Dutch House of Representatives in May 2010 by the Dutch Association for Lyme Patients (NVLP). One of the NVLP's goals is to bring the disease to the attention of the public, physicians, and the government. In addition to providing information on this topic, it organises Lyme patient support groups. The Citizen's Initiative was supported by more than 70,000 signatures.

On 27 April 2011, in response to this Citizen's Initiative, the Dutch House of Representatives formally requested the Health Council to prepare an advisory report on Lyme disease. The House asked the Council to determine the current level of knowledge in the areas of diagnosis and treatment, and to identify useful lines of enquiry for future research projects in this area.

1.2 The Committee's procedures

In response to the requests for advice, the Health Council has appointed a committee (details of the composition of this committee are given in Annex B). The Committee has taken a twin-track approach. The first track was to determine the current level of knowledge, mainly by means of a literature review. Also in the context of the first track, the Committee asked the Dutch Cochrane Centre (DCC) for an independent review of the literature on long-term antibiotic therapy.

The second track involved the perspectives of those affected. The Committee considered this issue to be so important that it commissioned VU University Amsterdam's Athena Institute to identify people's points of concern and their preferences in terms of future research projects. To this end, consultative exercises involving focus group surveys were carried out among various stakeholder groups (including patients and physicians). The Committee also interviewed physicians and held a hearing with the board of the Dutch Association for Lyme Patients (NVLP) in which it discussed a report drawn up by the NVLP in cooperation with *Stichting de Ombudsman* (the Dutch Ombudsman Foundation), entitled "*Ziekte van Lyme – een onderschat probleem*" (Lyme disease – an underestimated problem").

1.3 Structure of the advisory report

In Chapter 2, the Committee first explores the developments and initiatives around Lyme disease during the advisory process. In that same chapter, the Committee gives further details of the procedures used to elicit the perspectives of those affected. Chapter 3 deals with the cause and epidemiology of Lyme disease, while Chapter 4 gives details of the associated immune responses and disease symptoms. The Committee discusses the diagnosis of Lyme disease in Chapter 5 and covers treatment in Chapters 6 and 7. These chapters also address the points of concern regarding diagnosis and treatment that were identified in the focus group survey. Chapter 8 explores the general provision of information on Lyme disease, and the relevant aspects of physicians’ knowledge and training. Finally, in Chapter 9, the Committee puts forward a number of recommendations.

Chapter **2**

Recent initiatives and the advisory process

There has recently been a greater focus on Lyme disease in the medical/scientific domain, as well as in the public and political domains. A range of activities have been developed by patient associations, professional associations, and the Minister of Health, Welfare and Sport (VWS), together with various knowledge institutes and agencies. These initiatives have areas of commonality with the Health Council's advisory process.

Accordingly, in this chapter, the Committee outlines developments in the area of Lyme disease and indicates how it made use of these when drafting this advisory report. The Committee also describes its efforts to understand the experiences of stakeholders with Lyme disease, giving details of how it incorporated the perspectives of those affected into this advisory report.

At various points in this chapter passing reference is made to topics which the Committee explores in detail in later chapters.

2.1 Recent initiatives

Citizens' Initiative on Lyme disease

In recent years, the Dutch Association for Lyme Patients (NVLP) has made great efforts to bring the disease to the attention of the public, physicians, and the government. In addition to providing information and facilitating the patient support group, the NVLP submitted a Citizens' Initiative to the Dutch House of Representatives in May 2010.

The NVLP's Citizens' Initiative consists of an eight-point petition:

1. establishing an obligatory notification requirement or disclosure requirement for Lyme disease
2. modifying medical training programmes and providing physicians with further training about the *Borrelia* bacterium and the course of the disease, and especially about how to make a rapid clinical diagnosis of Lyme disease
3. the development of effective standardised test methods, which take account of aspects such as the range of different strains and the complex microbiology of *Borrelia* bacteria
4. establishing a centre of expertise for Lyme disease in the Netherlands, to coordinate research into topics such as the *Borrelia* bacterium, the disease course, and treatment
5. more research and a greater focus on the diagnosis and individual treatment of chronic Lyme borreliosis using antibiotics (including combination antibiotics) for longer periods and at higher doses
6. more research and a greater focus on the treatment of tick bite co-infections, which can exacerbate the clinical picture and make treatment more difficult
7. more wide-ranging dissemination of information, on a larger scale than before, about ticks and the possible consequences of tick bites, and issuing warnings to those visiting nature reserves and recreational areas
8. pushing for the development of a tick bite vaccine by exerting pressure at European level.

In April 2011, in response to this Citizens' Initiative, the Dutch House of Representatives requested the Health Council's advice on the current level of knowledge in the diagnosis and treatment of Lyme disease, and on research gaps in this area.

Actions taken by the Minister of Health, Welfare and Sport

In a letter to the Dutch House of Representatives, dated 20 June 2011, the Minister of Health, Welfare and Sport described the projects that she had assigned to the Centre for Infectious Disease Control Netherlands (CIb) and various other parties, to comprehensively tackle Lyme disease:

- the standardisation of existing diagnostic methods (CIb and the Dutch Society for Medical Microbiology (NVMM))

- research into the burden of disease associated with the various stages of Lyme disease and into the feasibility and advisability of a notification requirement for Lyme disease (CIb)
- keep abreast of developments in the field of vaccines against Lyme disease (CIb)
- research into the options for tick control in the Netherlands and into the effects of landscape management and modification on tick populations (CIb and Wageningen University, *Natuurmonumenten* (Society for the preservation of nature in the Netherlands), *Provinciale Landschappen* (Provincial Landscapes) and *Staatsbosbeheer* (the Dutch Forestry Commission))
- intensifying the provision of information and communication about how to prevent tick bites and how to remove ticks (CIb and municipal medical and health services, the Dutch Association for Lyme Patients, *Stigas* (an Occupational Health and Safety service), *Natuurmonumenten* (Society for the preservation of nature in the Netherlands), and *Staatsbosbeheer* (the Dutch Forestry Commission).

In her letter, the Minister pointed out that responsibility for the standardisation of testing procedures, for drawing up guidelines and for effective training (and in-service training) primarily rests with the professional groups involved. She also recommends that any hospitals planning to establish a specialised centre should do so in consultation with each other and with the CIb. The Minister also indicated that, partly in response to the Health Council's advisory report, she planned to commission research via the Netherlands Organisation for Health Research and Development (ZonMw). The goal of this research effort would be to expand knowledge in this area, thereby helping to improve the diagnosis and treatment of Lyme disease.

Review of Dutch Institute for Healthcare Improvement guideline on Lyme disease

In 2008, a guideline committee, supported by the Dutch Institute for Healthcare Improvement (the quality institute for healthcare), launched a review of the 2004 Lyme disease guideline. The revised guideline is evidence based. This means that a systematic search of the scientific literature was carried out, and that the publications found were assessed on the strength of the evidence. Based on the strength of the evidence, conclusions and recommendations were formulated for the guideline.

The Committee used the same public draft of the guideline that was submitted to the professional groups involved. At the time this advisory report was printed, the revised guideline had not yet been published. When it uses the term “guideline”, the Committee is referring to the draft guideline of July 2012.

Consensus Standing Committee on Laboratory Diagnostics for Lyme Disease

The Consensus Standing Committee on Laboratory Diagnostics for Lyme Disease was established in 2010, at the initiative of the National Institute for Public Health and the Environment (RIVM) and in cooperation with the Dutch Society for Medical Microbiology (NVMM). The aim of this partnership was to agree on which is the best test for diagnosing Lyme disease. The results of these consultations were published in 2012 in a special issue of the *Nederlands Tijdschrift voor Medische Microbiologie* (Dutch Journal of Medical Microbiology). The Committee makes use of these results in Chapter 5 of the advisory report.

British survey of research questions in the area of Lyme disease

While the advisory process was in progress, Lyme Disease Action (a British patient organisation) and the James Lind Alliance jointly identified the ten most important unanswered questions about Lyme disease.* In 2013, this top ten was brought to the attention of researchers and funding organisations.

The top 10 (Annex D) resulted from an internet survey to identify any remaining unanswered questions.[1] The collected questions making up this list have been assessed in terms of their relevance (those questions to which the answer was already known and any questions that are currently being researched were omitted). The remaining 26 questions were jointly prioritised by physicians and patients at a meeting staged and supervised by the staff of the James Lind Alliance.

While most of the questions in the top 10 concern the treatment of Lyme disease, there are also some relating to diagnosis. There are no questions about

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* Like the Athena Institute in the Netherlands, the James Lind Alliance (JLA) is an organisation that brings together patients and clinicians to jointly identify major uncertainties and unanswered questions about the treatment of disease (and the associated effects), and to pass these on to researchers. The JLA is part of the James Lind Initiative and is funded by the National Institute for Health Research. http://www.lindalliance.org/.

the doctor-patient relationship or about treatment, as the survey did not address such questions.

2.2 Activities within the advisory process

As mentioned in the introduction, many aspects of Lyme disease are still unclear. Within the professional group itself, there are differing views about the treatment of certain groups of patients. Also, much of the information on the internet is contradictory in nature. This situation leads to confusion and it damages patients' confidence in their physicians. Precisely because of this controversy, the Committee ruled that, in order to provide fully effective advice, they needed to understand the situation from the perspective of patients and physicians. What are these groups' points of concern regarding the diagnosis and treatment of Lyme disease and what are their priorities in terms of research? The Committee undertook a range of activities to elicit this information.

Hearing to consider the report produced by the Dutch Ombudsman Foundation/Dutch Association for Lyme Patients

In September 2011, the Dutch Association for Lyme Patients published the report that it had drawn up together with the Dutch Ombudsman Foundation.[2] This study was prompted by a desire to substantiate the Citizens' Initiative with hard data, particularly details of those patients described in the report as chronic Lyme patients. The study took the form of a written survey. Most of the subjects were members of the Dutch Association for Lyme Patients. The survey included questions about the exact sequence of events from the first complaints until treatment, about points of concern that arose during diagnosis, treatment, and encounters with physicians, and about the impact of Lyme disease on the performance of everyday activities.

The report sets out a number of recommendations, and preferences in terms of future research projects:

- more targeted scientific research into the cause, clinical manifestations, and treatment of the later and chronic stages of Lyme disease, and into improved diagnosis
- comparative research among different groups of Lyme patients may provide useful pointers for further research into the pathology of Lyme disease.

Three recommendations related to the provision of information and to developing and sharing knowledge and expertise:

- greater specialisation in medicine with respect to Lyme disease
- greater efforts to promote awareness among GPs, especially with regard to recognising the initial complaints
- invest in a centre of expertise where Lyme patients with chronic complaints can receive further treatment and where the staff are receptive to the patients' perspective.

This report was presented to the Committee in the course of a hearing. During this meeting, the Committee expressed reservations about the methodology underpinning the report in question. The Committee addressed several of the report's recommendations and suggestions in its considerations.

Focus group survey

With the aim of complementing the current level of knowledge based on medical and scientific literature, the Health Council commissioned VU University Amsterdam's Athena Institute to consult various stakeholder groups with a view to identifying points of concern, potential solutions, and potentially fruitful lines of research. The stakeholders in question were patients (or their parents), physicians, and high-risk groups. This consultative exercise provided first-hand insight into hot issues among the various groups. The Committee used these results in Chapter 9, when formulating recommendations for future research.

Focus group surveys are a tried and tested qualitative method for identifying perceived points of concern and for drawing up research agendas. The Athena Institute has extensive experience with this method and has carried out previous assignments on behalf of the Health Council.[3-5]

Focus groups (ranging in size from six to ten participants) make it possible to identify common personal and shared experiences associated with specific topics in an average of two hours. As they engage one another in conversation, the participants clarify their experiences, opinions, and the underlying arguments and make them more explicit, then go on to test their validity.

The focus group method provides a good balance between obtaining information in a formal, highly structured way and allowing scope for personal accounts. It involves horizontal (i.e. non-hierarchical) communication between all those involved. One drawback of this method is that, due to group dynamics or dominant participants, certain topics may receive a disproportionately high level of attention. One way of compensating for this effect is to get experienced moderators to supervise the groups, another is to set up more than one focus group.

A total of seven focus group meetings were held.[6] The groups consisted of:

- patients with short-term Lyme disease
- patients with long-term (or longer-term) Lyme disease (two groups)
- the parents of children with Lyme disease
- GPs
- professional practitioners at increased risk of Lyme disease
- those engaged in recreational activities that involve a high risk of Lyme disease.

A plan to set up a focus group of medical specialists was abandoned due to the logistical difficulties involved. Instead, nine medical specialists were interviewed.

The focus group participants were recruited through the Committee’s networks, and those of the Dutch Association for Lyme Patients and the Athena Institute.

The participants were first asked what points of concern they had encountered and then what research they felt was needed to solve these points of concern. Finally, they were asked to pick a Top Three from their list of research wishes. In Annex E, the Committee gives details of the Top Three for each of the focus groups.

The full report of the Athena Institute[6] was published as part of the background studies to this advisory report. These details can be found at the Health Council website.

Interviews with physicians

Partly in response to a request by the Dutch Association for Lyme Patients, interviews were held with a number of medical specialists, in parallel to the focus group surveys. These physicians had been recommended by the Dutch Association for Lyme Patients because of their openness to the issue of Lyme disease and its treatment. Three of these medical specialists also participated in the focus group surveys.

In the course of the interviews, it became clear that these physicians saw patients from all over the country. The main differences with “other” physicians were that these specialists took the time to talk to their patients about their complaints (rather than strictly limiting their consultations to ten to twenty minutes), that they often carried out more broad-based diagnostic testing, and that they were more likely to have good reasons for selecting treatments not listed in the guideline.

These physicians indicated that it is vital to sustain a dialogue with patients and to take the time to explain why they feel that a given patient either is or is not suffering from Lyme disease. Conversations about the conclusion that a patient is not (or is no longer) suffering from active Lyme disease can be particularly difficult. However, given enough time and attention, they do present an opportunity for patients to take an important step in their recovery process. These physicians had also found that patients can be receptive to the suggestion that it might be useful for them to see a psychologist or psychiatrist as part of their treatment. Provided that sufficient time is taken to explain the reasons for this approach, patients do not get the feeling that their complaints are not being taken seriously.

The physicians indicated that what they really needed was a network of specialist colleagues. This would allow patients to receive the treatment they need close to home, while making it possible for such treatment to be embedded in on-going scientific research.

They cited a range of topics for research:

- outcome research, based, for example, on an observational study of patients seen and, where applicable, treated by them
- clearer laboratory tests, the need for a gold standard
- research into the psychological and cognitive effects of neuroborreliosis
- research into the prevention of tick bites and into vaccines against *Borrelia* spp.

Including the perspectives of those affected in the advisory report

In its deliberations, the Committee addressed the recommendations and suggestions that emerged from the hearing, the focus group survey, and the interviews. At various points in the advisory report (starting in Chapter 5, on the diagnosis of Lyme disease) it makes specific mention of the perspectives of the various groups affected by this disease.

Chapter

3

Cause and epidemiology

In this chapter, the Committee explores the cause and epidemiology of Lyme disease in greater depth. The symptoms of this disease are described in the next chapter.

3.1 Origin and course

Lyme disease can develop after infection with a bacterium that is transmitted by ticks. In 1981, the microbiologist Willy Burgdorfer identified the bacterium that causes this disease, in the intestinal tract of a tick.[7] The bacterium was named after him: *Borrelia burgdorferi*. The disease is named after the town of Old Lyme in the United States, where a large number of people experienced joint complaints in the 1970s.[8]

The origin and course of Lyme disease are influenced by a number of factors.[9] That starts with the causative agent, as there are different species of Lyme bacteria. The Lyme disease caused by one species can have different clinical manifestations than the same disease caused by a different species. The distribution of these types of bacteria varies. In the United States, for example, the disease is caused by just a single species, whereas in Europe many different species are involved. As a result, patients from different countries sometimes exhibit different disease symptoms.

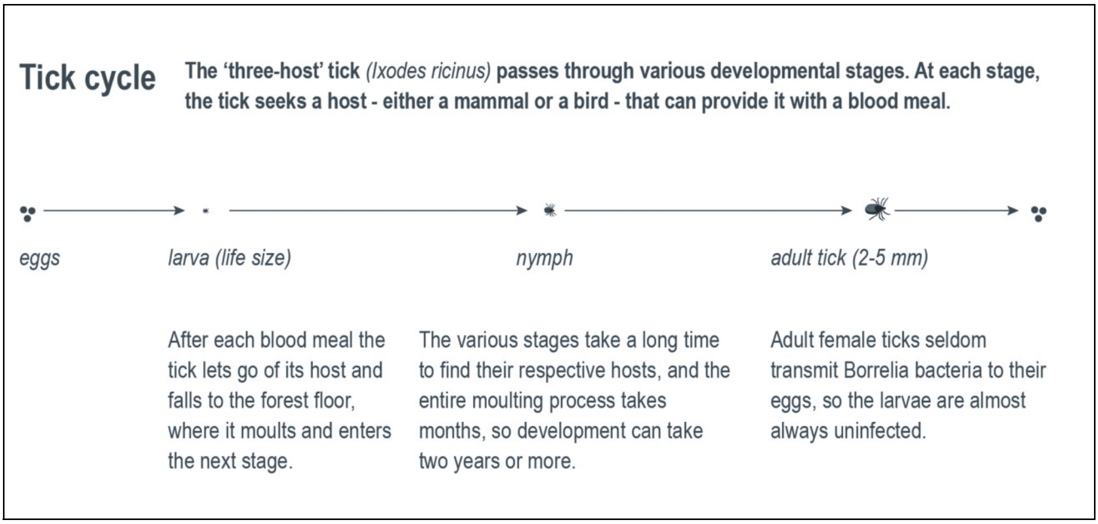
A second factor is the risk of infection. This risk is determined by the presence and activity of ticks, by their infection rate, and – above all – by human exposure to ticks. Factors such as landscape type and season also contribute to the high level of variation in the risk of human infection.

The third factor occurs post-infection. The bacterium can affect several different organ systems, and the disease symptoms can vary from one patient to another. Lyme disease has a number of stages and the prognosis is, to some extent, dependent on the stage at which treatment commenced.

3.2 Transmission by the sheep tick

Small animals (usually arthropods) that are capable of transmitting pathogens to animals or humans are referred to as vectors. One example is the mosquito that transmits the malaria parasite. Another is the rat flea that transmits the plague bacterium. The causative agent of Lyme disease is also transmitted by a vector. In the Netherlands, that is the sheep tick (*Ixodes ricinus*).

Ticks are arachnid parasites that feed on various animal species and on humans. In this way, they transmit bacteria from one animal to another, and from animals to humans. The sheep tick occurs throughout the Netherlands. It lives in tall grass and bushes in forests, dunes, meadows, gardens, parks and heathlands.[10,11]



Tick cycle **The ‘three-host’ tick** *(Ixodes ricinus)* **passes through various developmental stages. At each stage, the tick seeks a host - either a mammal or a bird - that can provide it with a blood meal.**

After each blood meal the tick lets go of its host and falls to the forest floor, where it moults and enters the next stage.

The various stages take a long time to find their respective hosts, and the entire moulting process takes months, so development can take two years or more.

Adult female ticks seldom transmit Borrelia bacteria to their eggs, so the larvae are almost always uninfected.

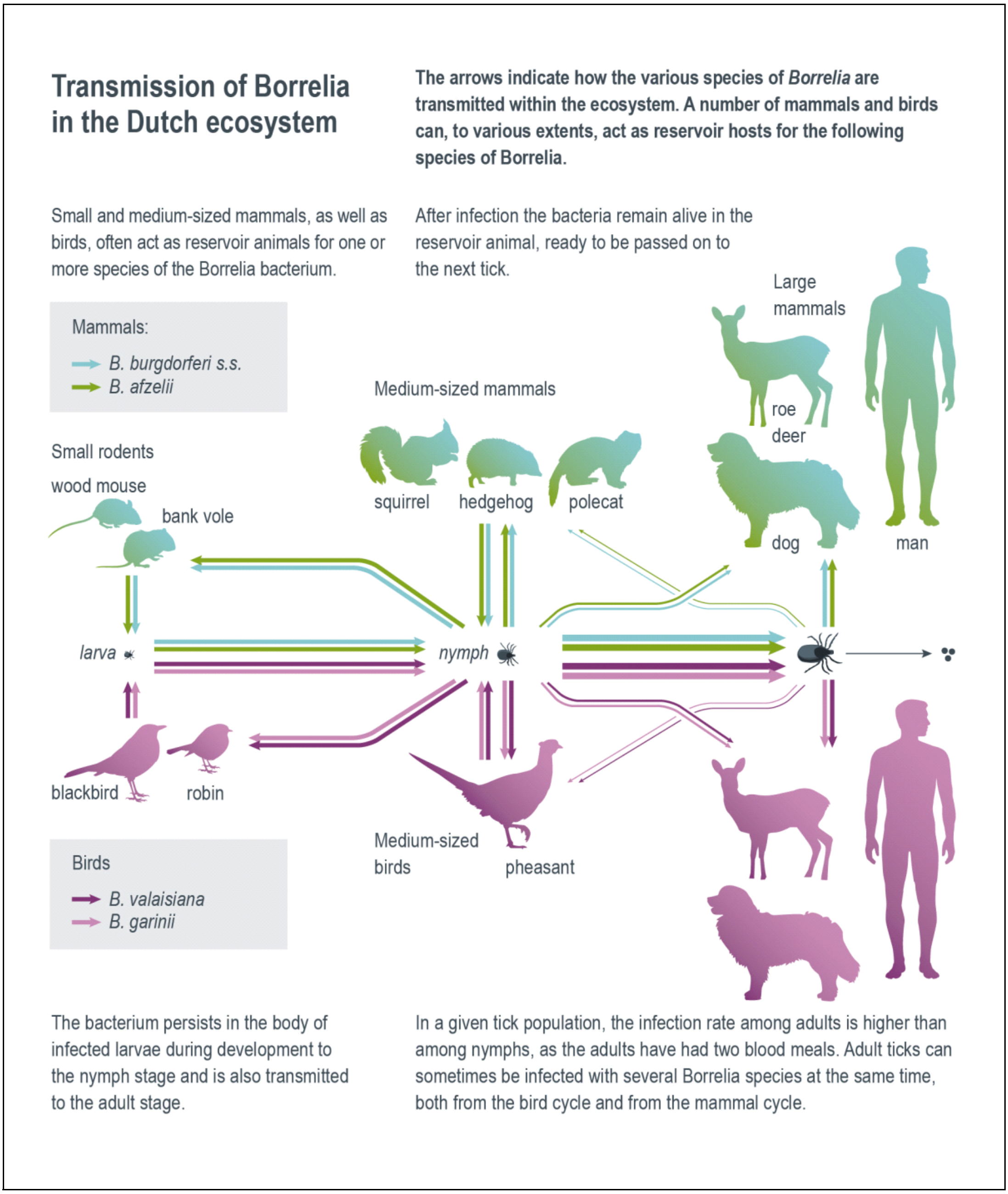
Figure 1a Life cycle of the tick.

Ticks start their life cycle as eggs in leaf litter on the ground. The larvae emerge from the eggs and eventually moult to become nymphs, which go on to become adult ticks.[12] This cycle is estimated to take two to six years, in temperate climates. Remarkably, this is generally longer that the lifetimes of some of the tick's hosts, such as mice and birds.[13,14]

Before moulting, ticks take a "blood meal" from an animal or a human. When they are fully engorged with blood, they fall to the ground once again. When taking a blood meal, ticks can become infected with the Lyme bacterium. At their next blood meal, they in turn can transmit it to the new host. Humans, too, can become infected with the *Borrelia* bacterium. However, they are considered to be "accidental hosts" rather than "reservoir hosts" as they play no significant part in transmitting the bacterium to other ticks.

Once ticks have attached to a host it usually takes some time before the Lyme bacterium is transmitted. Accordingly, the host's risk of infection can be greatly reduced if the tick is removed in good time. After taking a final blood meal, adult female ticks lay their eggs in the soil and then die. It is almost impossible for the Lyme bacterium to be transmitted via the eggs.

Ticks become active when the temperature rises above 7°C[15], so most people are bitten between March and October. The peak period for tick bites is in the months of May and June. This is when most ticks are active and also when people are engaging in active outdoor pursuits in natural surroundings more frequently and for longer periods of time. In 2009, more than a million people in the Netherlands were bitten by ticks.[10,11]The *Tekenradar* (Tick Radar) study found that 22 percent of the ticks sent in by members of the public during 2012 were infected with *Borrelia*. Just three percent of those bitten by an infected tick went on to develop Lyme disease. In 80 percent of these cases the disease was limited to *erythema migrans* (EM), a characteristic ring-shaped rash that is also known as bullseye rash (see Chapter 4).[10,16]



Transmission of Borrelia in the Dutch ecosystem

The arrows indicate how the various species of *Borrelia* are transmitted within the ecosystem. A number of mammals and birds can, to various extents, act as reservoir hosts for the following species of Borrelia.

Small and medium-sized mammals, as well as birds, often act as reservoir animals for one or more species of the Borrelia bacterium.

After infection the bacteria remain alive in the reservoir animal, ready to be passed on to the next tick.

The bacterium persists in the body of infected larvae during development to the nymph stage and is also transmitted to the adult stage.

In a given tick population, the infection rate among adults is higher than among nymphs, as the adults have had two blood meals. Adult ticks can sometimes be infected with several Borrelia species at the same time, both from the bird cycle and from the mammal cycle.

Figure 1b Transmission of *Borrelia* in the Dutch ecosystem.[86]

3.3 Bacteria that cause Lyme disease

Different species

Lyme disease is caused by various species of bacteria in the genus *Borrelia*. This is a spirochaete, a spiral-shaped bacterium. The *Borrelia* species are collectively referred to as *Borrelia burgdorferi sensu lato* (“sensu lato”: “in the broad sense”). Only a few *Borrelia* species are known to cause Lyme disease in humans. These are *Borrelia burgdorferi sensu stricto* (in the strict sense, hereinafter referred to as *B. burgdorferi s.s.*), *Borrelia garinii*, *Borrelia afzelii*, *Borrelia spielmanii* and *Borrelia bavariensis*.[17] In the United States, *Borrelia burgdorferi s.s.* is the sole causative agent of Lyme disease. In Europe, however, all of the above-mentioned causative agents occur, the most common being *B. afzelii* and *B. garinii*.[13,18]

Although the main characteristics of Lyme disease are the same on both continents, the different causative agents do give rise to variation in the appearance and manifestation of the disease. Skin disorders are more often associated with *B. afzelii* infections, while *B. garinii* more frequently gives rise to neurological complaints, and *B. burgdorferi s.s.* is mainly associated with arthritis.[12,19,20]

In this advisory report, the Committee uses the term “the Lyme bacterium” when referring to the Lyme disease pathogen in a general sense. Where necessary, it refers to the various *Borrelia* species by name.

Different disease symptoms

When ticks are gorging on blood, the Lyme bacterium migrates away from the tick’s gut and moves into its new host. During the first few weeks or months after infection, the Lyme bacterium remains in the skin. After that it can spread throughout the body. During this process, different species of Lyme bacteria appear to have different ‘tissue preferences’. For instance, *B. burgdorferi s.s.* (which mainly occurs in the United States) spreads primarily through the bloodstream, while *B. garinii* (which mainly occurs in Europe) spreads primarily along nerve pathways.

These different preferences are reflected in the variation seen in the most striking disease symptoms on these continents (see Chapter 4). Many hypotheses have been put forward and several animal studies carried out, yet the mechanism by which *Borrelia* causes such different disease symptoms (or the course of pathogenesis) is still poorly understood.[21-24]

3.4 The prevalence of Lyme disease

For various reasons, it is difficult to determine the frequency of Lyme disease in the Netherlands. This is because the disease has a range of clinical manifestations, and some patients may present with uncharacteristic complaints. Some cases will take a long time to be diagnosed, if at all.[25] Moreover, laboratory tests cannot always show whether patients have had an infection in the past, or whether they still have an active infection.

The most characteristic symptom of Lyme disease, *erythema migrans* (EM), can be a useful indicator in this regard. This is a ring-shaped, red colour change on the skin. In 2009, the incidence of EM in the Netherlands was estimated at 134 cases per 100,000 inhabitants.[26] The actual incidence of Lyme disease could be even higher, as EM does not occur in all patients. For instance, a Swedish study showed that the appearance of EM was recorded in the disease histories of just 77 percent of patients with Lyme disease.[27]

In recent years, the number of individuals consulting their GP with EM rose from 17,000 in 2005 to 22,000 in 2009.[10] This rise may indicate an increase in Lyme disease in the Netherlands, but it might also be due to increased public awareness of this disease.

3.5 Other micro-organisms found in ticks

Ticks can carry a range of different micro-organisms. In addition to *Borrelia* species, various other bacteria and protozoan parasites have been found in Dutch ticks.[28] These include bacteria of the genera *Rickettsia* and *Anaplasma* (also known by its old name of *Ehrlichia*), and the protozoan parasite *Babesia*.

Several of these micro-organisms can cause disease in humans.[28] In the case of the bacteria, this usually involves flu-like disease symptoms, such as fever and muscle cramps. Babesia infections are usually mild, but they can have a more severe course in individuals with weakened immune systems.

It is not clear, however, whether the species found in the Netherlands actually cause disease. There are virtually no known cases of disease involving infections by the above-mentioned species that were contracted in the Netherlands.[29] Also, little is known about the extent to which co-infections (involving various micro-organisms transmitted by ticks, either simultaneously or via a series of bites from different ticks) occur in humans. Nor is it known how infection with another micro-organism affects the course of Lyme disease. This might result from the fact that diagnostic laboratory tests for these other tick-borne micro-organisms are not universally available.

3.6 Conclusion

Lyme disease is caused by species of bacteria in the genus *Borrelia*, which are transmitted to humans by sheep ticks. The prevalence of *Borrelia*-infected ticks varies from one part of the Netherlands to another. However, the prevalence and pathogenic characteristics of other micro-organisms found in sheep ticks are relatively poorly understood.

The Committee feels that it is important to obtain a better understanding of the significance of other tick-transmitted infections, not just of Lyme disease alone. Accordingly, it recommends that further research be carried out in this area. Secondly, the Committee recommends that steps be taken to improve the diagnosis of micro-organisms transmitted by ticks. The Committee will revisit the issue of the diagnosis of Lyme disease in Chapter 5.

Chapter

4

Immune responses and disease symptoms

The human body responds to infection with the Lyme bacterium by mounting an immune response. Disease symptoms may also develop soon after infection or at a later time. In this chapter, the Committee summarises both scenarios. Here, the Committee makes frequent reference to a review article on Lyme disease that was published in the British journal *The Lancet*, in 2012.[18]

4.1 Immune responses

Following infection with the Lyme bacterium, the host mounts an immune response aimed at eliminating the pathogen. This reaction involves a range of elements, including cells of the immune system (cellular immune response) and antibodies (humoral immune response), which are proteins produced by the immune system.[18] One type of cellular response involves macrophages, which engulf the bacteria and render them harmless. Macrophages are just one of the cell types involved in an immune response. These macrophages can engulf many species of micro-organisms. Antibodies, on the other hand, are produced by B cells, and are specifically generated against the infecting bacterium.

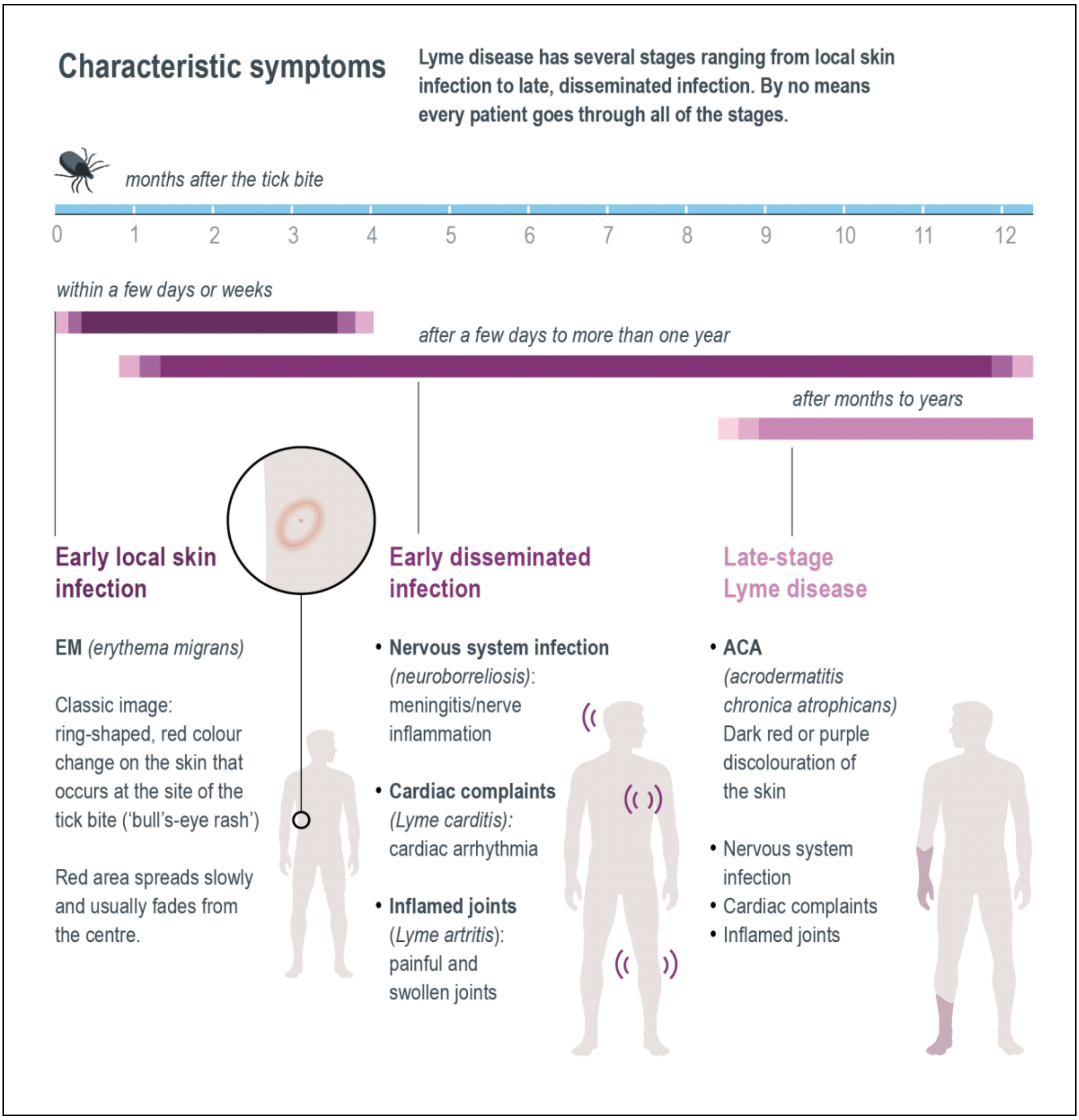
Even with this combined cellular and humoral immune response, the body does not always succeed in eliminating the Lyme bacterium. There are various reasons for such bacterial persistence. The first of these is that the bacteria may accumulate at sites in the body that are less easily accessible to the immune system, such as the joints and the brain,[30] and in the extracellular matrix, the space between body cells.[18] A second reason may be that the Lyme bacterium reduces its ‘visibility’ to the immune system, for example, by reducing the expression of those parts (antigens) that are targeted by antibodies, by increasing the variety of these antigens, or by expressing proteins that the immune system cannot easily handle.[18] The Lyme bacterium can also evade the immune system by binding host proteins to its surface, thus disguising itself as ‘self’(i.e. normal body tissue).[18,21-24]

4.2 Characteristic disease symptoms

Lyme disease has several stages ranging from early onset, local skin infection to late, disseminated infection. The various stages are associated with different disease symptoms. When discussing disease symptoms, the Committee distinguishes between symptoms that are characteristic of Lyme disease (e.g. EM), and complaints that are not characteristic of Lyme disease (e.g. fatigue).

By no means every patient goes through all of the stages, or is aware of having gone through them. In this way, people are generally only aware of the first stage (EM), and many patients with Lyme arthritis do not remember having had any other clinical manifestations of the disease.[18] Moreover, there is considerable variation in the time taken for complaints to develop following a tick bite. For instance, the complaints associated with early local infection appear a few days to a month after the bite, while early disseminated infections take a few weeks to several months to appear. The complaints associated with late-stage Lyme disease take months or even years to develop (see Figure 2).[31]

Here, the Committee discusses the various effects and complaints associated with infection in order of appearance (or potential appearance).



Characteristic symptoms

Lyme disease has several stages ranging from local skin infection to late, disseminated infection. By no means every patient goes through all of the stages.

months after the tick bite

within a few days or weeks

after a few days to more than one year

after months to years

Early local skin infection

EM *(erythema migrans)*

Classic image: ring-shaped, red colour change on the skin that occurs at the site of the tick bite ('bull's-eye rash')

Red area spreads slowly and usually fades from the centre.

Early disseminated infection

- **Nervous system infection** *(neuroborreliosis)*: meningitis/nerve inflammation
- **Cardiac complaints** *(Lyme carditis):* cardiac arrhythmia
- **Inflamed joints** (*Lyme artritis*): painful and swollen joints

Late-stage Lyme disease

- **ACA** *(acrodermatitis chronica atrophicans)* Dark red or purple discolouration of the skin
- Nervous system infection
- Cardiac complaints
- Inflamed joints

Figure 2 Characteristic symptoms of Lyme disease.

Local skin infection

As stated above, *erythema migrans* is the most characteristic symptom of Lyme disease. EM develops within a few days or weeks after the tick bite.[32] The classic image of EM is a ring-shaped, red colour change on the skin that occurs at the site of the tick bite. The bacteria are located at the spreading edges of the reddened area of skin, from where they ‘creep’ ever further outwards. In this way, the reddened area spreads slowly, fading from the centre and disappearing after a few weeks to a year.[13,33]

However, EM can adopt entirely different shapes and it may not necessarily fade from the centre outwards. In rare cases, instead of an EM, a lymphocytoma may develop. These blue-red swellings, a few centimetres acrosìs, usually appear on the ear lobes (in children) or the nipples (in adults).[13,32,36] In Europe, EM occurs in 60 to 80 percent of individuals with Lyme disease.[12]

Early disseminated infection

The Lyme bacterium can leave the skin, enter the bloodstream and then spread throughout the body. At this point it is described as a disseminated infection. In this phase of the disease, clinical manifestations of infection may appear in the nervous system (neuroborreliosis), the joints (Lyme arthritis) and – less often – the heart (Lyme carditis). Patients may also develop multiple EM, involving the simultaneous development of several red rings on the skin.[32]

Neuroborreliosis

Neuroborreliosis is when the infection has spread to the nervous system. Early neuroborreliosis can lead to the development of meningitis. Inflammation of the cranial nerves can lead to paralysis of the facial muscles (facial palsy) and double vision. Inflammation of the spinal nerves (radiculitis) can cause severe pain in the arms, legs or torso, and to changes in touch, movement and reflexes in the affected area.[32,34,36]

Lyme arthritis

Joint inflammation can also occur as a result of an early disseminated infection. This usually involves the painful swelling of one or several major joints, such as the knee.[8,35] These disease symptoms are usually self-limiting, but they can sometimes persist for periods of up to several months.[36] Lyme arthritis may involve autoimmune reactions, in which immune system components that have been activated by the infection start to attack normal body tissue. In this way, the immune response can continue even after the bacteria have been eliminated, causing the disease symptoms to persist.[21]

Lyme carditis

Heart defects are rare clinical manifestations of early disseminated Lyme disease. The most common symptom is an atrioventricular block.[13] This is a disorder affecting the transmission of electrical impulses across the heart, leading to the development of a cardiac arrhythmia.

Late-stage Lyme disease

The most characteristic symptom of late-stage Lyme disease is *acrodermatitis chronica atrophicans* (ACA).[13,18] ACA is a dark red or purple discolouration of the skin, often appearing on the extensor surfaces of the limbs. In the early stages, the skin is slightly thickened and is warm to the touch. Later, however, the skin starts to get thinner, developing a ‘papery’ feel.

The symptoms cited in connection with early disseminated Lyme disease (neuroborreliosis, Lyme arthritis and Lyme carditis) can also occur in late-stage Lyme disease.[18]

4.3 Uncharacteristic complaints

At different stages of the disease, Lyme disease patients may experience complaints such as fever, muscular pain, painful joints, headaches, a stiff neck, lethargy, fatigue, and concentration problems.[13,33] These complaints tend to be most prominent at the start of an infection. However, they can also occur in the later stages of the disease and can even persist after treatment. These complaints are not characteristic of Lyme disease. They commonly occur during or after other diseases (including infectious diseases).

4.4 Persistent disease symptoms following treatment

In Chapter 6, the Committee explores the use of antibiotics to treat Lyme disease patients. It prefaces this topic by pointing out that disease symptoms can persist even after treatment.

The vast majority of patients with Lyme disease are cured by antibiotic therapy. However, some patients still exhibit disease symptoms even after they have completed a course of antibiotic therapy. Various causal factors can account for the persistence of these complaints. In the case of characteristic symptoms, the problem may be therapy failure, residual damage, or a reinfection. Post-treatment uncharacteristic complaints, such as severe fatigue, are quite common in infectious disease cases. Reports indicate that the same is true of Lyme disease. The mechanisms which give rise to the latter complaints are unknown.

4.5 Conclusion

Lyme disease is an infectious disease that is associated with a variety of characteristic symptoms and uncharacteristic complaints. It has a complex pathogenesis, which is not yet fully understood. There is considerable variation in the time taken for disease symptoms to develop following a tick bite. By no means every patient goes through all of the stages, or is aware of having gone through them. Most patients only go through the first stage, partly as a result of treatment being administered in good time.

Following infection with the Lyme bacterium, the host mounts an immune response aimed at eliminating the pathogen. This reaction involves a range of elements, including cells of the immune system (cellular immune response) and antibodies (humoral immune response), which are proteins produced by the immune system.

Chapter

5

Making a diagnosis

It is a fairly simple matter to diagnose ‘Lyme disease’ when the patient presents with EM and remembers being bitten by a tick. In such cases, it is certain that the patient has Lyme disease. Accordingly, further tests are not required and antibiotic therapy can be started immediately.[12,18,37] However, the situation is not always as straightforward as this. Many patients cannot recall being bitten by a tick, so no clear starting point for the disease process can be identified. The situation is further complicated by the fact that Lyme disease can manifest itself in many different ways, involving a range of characteristic symptoms and uncharacteristic complaints. If it is not possible to make a diagnosis of Lyme disease (or to exclude such a diagnosis) based on the case history and a physical examination, then additional testing will be needed, initially taking the form of laboratory tests.

In this chapter, the Committee discusses the diagnostic options, and evaluates the tests that are available for this purpose. It concludes with a discussion of points of special interest in diagnosing Lyme disease.

5.1 Case history and physical examination

A carefully compiled case history and a physical examination, together with a focus on the disease history, are essential elements in reaching a diagnosis of Lyme disease. Accordingly, it is important to know whether the patient has been bitten by a tick and, if so, when and where this occurred (possibly many months before the symptoms appeared, during a holiday abroad for example). A second point for consideration is whether the patient has had Lyme disease in the past and, if so, whether they received treatment at that time.

Another issue, when considering the disease symptoms, is the extent to which characteristic symptoms (EM, arthritis, facial paralysis) and uncharacteristic complaints (fever, muscular pain, ‘flu-like symptoms’, fatigue) are involved. After all, uncharacteristic complaints can be produced by a wide range of infectious and non-infectious diseases.

A physical examination may reveal characteristic abnormalities, such as EM or borrelial lymphocytoma, which – even if patients do not remember being bitten by a tick or if they have negative serological assay results – nevertheless constitutes proof of Lyme disease. However, while EM is certainly characteristic of the disease, recognising it in practice is often difficult. Most textbooks show the most typical type of EM, so red skin lesions with a different shape or aspect are often not recognised as having been caused by a tick bite. As a result, such cases go untreated.

5.2 Diagnostic tests

5.2.1 Theoretical background

Available methods

Traditionally, in the case of suspected bacterial infections, the first test to be carried out is to determine whether or not bacteria derived from bodily materials can be grown in culture. However, culturing the Lyme bacterium is extremely difficult and time consuming. As a result, the options for growing the Lyme bacterium in the laboratory are very limited.[37]

Accordingly, lab staff are compelled to make use of alternative methods. In this context, the Committee discusses examples of indirect and direct tests. The former is a serological assay procedure used to detect antibodies generated by the patient in response to the bacterium. The latter involves testing for the presence of the bacterium’s genetic material. A serological assay is the main method used to confirm Lyme disease.

The Committee first explores the theoretical background to these tests. The importance of this approach is that it enables the Committee to better describe the limitations of the tests involved.

Predictive value

The purpose of laboratory testing is to obtain further information from tests on bodily materials (e.g. blood or urine) to make or to exclude a diagnosis of Lyme disease. Sensitivity and specificity are of great importance in this connection. The sensitivity of a medical test is the percentage of true positive results among diseased individuals, while specificity is the percentage of true negative test results among non-diseased individuals.

Partly based on the frequency of occurrence of the disease in question, sensitivity and specificity can be used to calculate the chance that a negative test result really means that the patient *does not* have the disease or infection for which they are being tested (negative predictive value) and the chance that a positive test result really means that the patient *does* have the disease or infection for which they are being tested (positive predictive value).

Virtually every laboratory test, including those for Lyme disease, generates false positive and false negative results. In general, the better the sensitivity of a test (relatively low number of false negative results) the poorer its specificity (relatively high number of false positive results). Conversely, the better the specificity the poorer the sensitivity.

Importance of the a priori probability

The occurrence of false positive and false negative results has implications for the significance of the test results. The a priori probability of a disease is an important factor in this context. As examples of an a priori probability, the Committee cites the chance of Lyme disease occurring in an individual who cannot recall having been bitten by a tick and who lives in an urban environment, in which case the a priori probability is low. The situation is different in the case of a forester who has recently been bitten by a tick, in which case the a priori probability is high.

The problem with the use of laboratory tests in the case of individuals with a very low a priori probability is that the number of false positive results tends to be much larger than the number of true positive results. The effect of using diagnostic laboratory tests under circumstances such as these is that there is a very low probability of someone with a positive test result actually having the disease for which they are being tested (the positive predictive value of the test result).[37] In such cases, it makes little sense to use diagnostic laboratory tests.

In compliance with the Dutch Institute for Healthcare Improvement's guideline, the Committee emphasises that consideration should be given to the a priori probability of Lyme disease when deciding whether or not to have additional tests (including laboratory tests) carried out.[37]

5.2.2 *Serological assay*

What the assay involves

The formation of antibodies by B cells is one of the ways in which the body reacts to invading micro-organisms, in this case, the Lyme bacterium. Antibodies are protein molecules that are able to recognise and bind to that part of the bacteria against which they were generated (the antigen). Based on their structure, antibody molecules are divided into classes (and subclasses). During an infection (and this applies to Lyme disease too), immunoglobulin M (IgM) antibodies are usually the first to be generated, followed by IgG antibodies.

A serological assay checks for the presence of these antibodies in blood or cerebrospinal fluid, for example (the latter is tested in cases of suspected neuroborreliosis, see section 4.2.2). The presence of antibodies is detected in the laboratory by binding them either to whole bacterial cells or to isolated antigens, then rendering the bound antibodies visible. The first test used in diagnostic procedures for Lyme disease is usually Enzyme Linked Immunosorbent Assay (ELISA).

In the event of a positive ELISA test result, it is standard procedure to seek confirmation with a second serological laboratory assay, known as the immunoblot. This technique separates out the various antigens of the Lyme bacterium, making it possible to identify the specific antigens targeted by the detected antibodies. If the immunoblot also reveals the presence of antibodies, the test result is considered to be positive.

Research results

Studies carried out in other countries show that at an early stage in the infection process, the sensitivity of serological assays is relatively low, even if both IgM and IgG antibodies are being targeted. In cases of EM, sensitivity is around fifty percent, while in cases of acute neuroborreliosis it is eighty percent.[38-41] At a later stage of the infection process, in patients with acrodermatitis chronica atrophicans or arthritis, for example, sensitivity approaches one hundred percent.[38,39,42-46] If a serological assay is repeated on a second blood sample, early in the disease process (in patients with EM), this leads to an increase in sensitivity.[41] These results reflect the ‘window period’ between the start of the infection and the initial production of antibodies. The Committee will return to the topic of the window period in the next section.

In October 2012, the Dutch Consensus Standing Committee on Laboratory Diagnostics for Lyme Disease published the results of research into the situation in the Netherlands. The impression that serological assays become increasingly sensitive later in the disease process was confirmed.[47] Remarkably, there is substantial variation between the results obtained by the various participating laboratories, especially with regard to blood samples taken from patients in the early stage of the disease.[47,48] A similar degree of variation was found with regard to specificity.[47] The Consensus Standing Committee attributes this variation in sensitivity and specificity to the large number of different test kits being used in Dutch laboratories.[47,48]

Diagnostic limitations

Resulting from the window period

A serological assay is an indirect test method. Rather than detecting the pathogen itself, it focuses on a bodily response (antibody generation) to the infection. It takes time to develop antibodies in response to an infection. In the case of Lyme disease, this means that a significant proportion of patients with EM, which occurs at an early stage of the infection process, have not yet been able to generate antibodies.[13]

In Lyme disease, it generally takes two to eight weeks for the antibodies generated against the pathogen to reach readily detectable levels (the window period).[37,46] From that point onwards, the vast majority of patients have sufficient antibodies to the Lyme bacterium in their blood to give positive test results in the ELISA and immunoblot assays.

Once they have been generated, antibodies can remain detectable for many years after the infection has been cleared. Accordingly, the presence of antibodies does not necessarily indicate the presence of an active infection. Nor, indeed, does the presence of antibodies provide complete protection against the disease. This means that those who have had an infection in the past and who have antibodies in their blood can be re-infected and become ill once again.[18]

The window period accounts for the fact that tests carried out early in the disease process, using serological techniques, can produce negative results. For various reasons, it may therefore be useful to take a second blood sample a few weeks later and to test this for antibodies.[37] Thus, if antibodies were absent from the first blood sample but present in the second, this is a clear indication of an active infection. Another indication could be a shift from IgM antibodies (which form first) to IgG antibodies (which form later).

The possibility cannot be excluded that some patients with active Lyme disease will still have no detectable antibodies at even longer intervals after infection. Some refer to this condition as seronegative Lyme disease. However, the Committee considers this to be extremely unlikely in individuals whose immune systems have not been compromised.

The scientific literature describes a small number of seronegative patients with Lyme disease. In such cases doubt is often cast on the reliability of the methods used[37,49], in others the individuals in question had compromised immune systems.[50] The diagnosis of Lyme disease in everyday practice is often based on the results of a serological assay. As a result, it is difficult to determine how often cases of active Lyme disease generate negative results. Accordingly, it is difficult to draw formal conclusions on this issue. However, as few if any patients with characteristic symptoms lack antibodies to the Lyme bacterium, the Committee assumes that this is a very rare phenomenon.

Another effect of the window period is that successful early treatment with antibiotic therapy can lead to limited antibody development.[37] After all, the pathogen that induces the antibodies is no longer present in the body. Accordingly, laboratory tests on blood from a Lyme patient who received early treatment may yield a negative test result, even though the patient had been infected. In such cases, there is little point in carrying out a serological assay.

As a result of a serological scar

Once antibodies have been created they do not simply disappear again, even if the Lyme bacterium has been eliminated with the aid of the immune system and/or by means of antibiotic therapy. Antibodies often remain detectable for prolonged periods of time, in some cases for many years. For this reason they are referred to as a serological scar.

In this way, up to ten percent of people in the Netherlands have antibodies to the Lyme bacterium in their blood as a result of a past infection, which in some cases may have gone unnoticed.[51,52] This is more common among those who are at high risk of infection with the Lyme bacterium (due to their professional activities), possibly affecting up to twenty percent of such groups.[27,53]

Accordingly, once a patient has generated antibodies, repeating the test usually provides no further useful information. Thus, it cannot be concluded that a patient currently has an infection solely on the basis of a single positive serological assay result.

As a result of cross-reactivity

Another limitation of serological assays is due to cross-reactivity. In practice, it has been found that, in addition to recognising the antigen against which they were generated, antibodies sometimes recognise other, similar, structures (i.e. they cross-react with these structures). This can result in a false positive ELISA for Lyme disease in individuals who do not actually have this disease. In general, IgM antibodies tend to exhibit more cross-reactivity than IgG antibodies. In most cases, an immunoblot can show whether or not any cross-reactivity is taking place.

5.2.3 *Polymerase Chain Reaction*

The Polymerase Chain Reaction or PCR can detect a pathogen's genetic material (DNA in the case of the Lyme bacterium) in skin or joint biopsies, in cerebrospinal fluid or in synovial fluid, for example. Thus, PCR is a direct test. PCR is a highly sensitive assay, theoretically capable of detecting a single copy of the bacterium's DNA. Despite this great sensitivity, however, PCR also has its limitations.

Compared with the serological assays, PCR for Lyme disease is still in its infancy. To date, all of the tests used in the Netherlands have been developed by the testing laboratories themselves, and documentation and validation are not always available.[37]

In view of this, the Consensus Standing Committee on Laboratory Diagnostics for Lyme Disease has stated that PCR is still of limited value in the diagnosis of Lyme disease.[54] The authors of the Dutch Institute for Healthcare Improvement's guidelines recommend the use PCR on skin samples, joint material and cerebrospinal fluid (CSF), but only in cases where, based on clinical complaints and the results of serological assays, there is still some doubt about the diagnosis.[37] They advise against the use of PCR on the blood and urine of patients suspected of having Lyme disease. This is because the tests have not been clinically validated nor, as comparative studies have shown, are they reproducible between separate laboratories. The Committee concurs with this view.

5.2.4 *Other diagnostic tests*

Some laboratories use other tests, in addition to serological assays and PCR. Examples of this are various forms of microscopy, and histopathology, tests to detect the presence of antigen, and the lymphocyte transformation test. More recent tests are based on the detection of complexes of Lyme bacterium antigens and the corresponding antibodies in patients' blood, or on the detection of messenger molecules (cytokines) at different phases of the infection.[55] Further development of the latter test could lead to a test capable of distinguishing between an active infection and a past infection.

Scientific studies have found that a number of these tests (in particular, the light microscopy test and lymphocyte transformation test) could neither be standardised nor reproduced. For this reason, the Committee advises against using them. In terms of reviews of published research data on these techniques, the Committee restricts itself to a reference to the Consensus Standing Committee on Laboratory Diagnostics for Lyme Disease and to the Dutch Institute for Healthcare Improvement's guideline.[37,54,55]

Other methods, such as histopathological examination, can help to support a clinical diagnosis of acrodermatitis chronica atrophicans, for example.[37] More recently developed methods, such as the test for cytokines, have not yet been sufficiently studied to recommend their use as standard laboratory tests.

5.2.5 *Testing ticks for signs of infection with Borrelia*

The transmission of the Lyme bacterium from ticks to humans is a fundamental aspect of Lyme disease. This has led to the development of a test capable of determining whether ticks found on people are infected with the bacterium.

Even if a tick is found to be infected, this has limited predictive value in terms of the risk that the individual bitten by that tick will actually develop an infection.[37] It therefore makes little sense to test ticks for the presence of the bacterium. Moreover, commercial home test kits are already being marketed while questions remain about how they work and about their reliability. For this reason, the Committee advises against the use of such kits.

5.3 Points of special interest from a scientific perspective

Even where the best use is made of a combination of case history, physical examination, and (where applicable) laboratory tests, it can sometimes still be difficult to make a diagnosis of Lyme disease (or to exclude such a diagnosis) as this disease can present in a variety of ways. For instance, the disease produces facial paralysis more often in children than in adults. EM also can be difficult to recognize where the presentation differs from the typical red ring (bullseye) shape, and rarer symptoms of Lyme disease, such as a lymphocytoma on an earlobe or nipple may be overlooked. Finally, the disease often presents as arthritis or neuroborreliosis without first producing EM.

Here, the Committee cites several ways of boosting the chances of a clear diagnosis. Finally, it indicates the course of action to take if the diagnostic path fails to produce a satisfactory outcome.

Standardisation of laboratory tests

The Consensus Standing Committee on Laboratory Diagnostics for Lyme Disease sees the variation in laboratory tests for Lyme disease in the Netherlands as undesirable. This is because patients – especially those with early-stage Lyme disease – may get a negative test result from one laboratory and a positive result from another.[48,49] The Consensus Standing Committee on Laboratory Diagnostics for Lyme Disease makes recommendations aimed at optimising the test strategies used and at creating greater standardisation in the interpretation of diagnostic laboratory tests.[48] The Committee concurs with the Standing Committee's position on this matter, and urges the swift and mandatory standardisation of tests used in the Netherlands.

Possible new test

The Committee has stated that, once generated, antibodies often remain detectable long after the infection has passed. For this reason, in practice, repeating serological assays usually provide no further useful information. A study of changes in antibody titres over time, however, has shown that antibody concentrations against C6 peptide decline more rapidly in patients with early-stage Lyme disease than in those with late-stage Lyme disease.[56] This study could lead to a test capable of distinguishing between an active infection and a past infection.

Diagnosis based on a complete picture

It is often difficult to diagnose Lyme disease, but it can become still more difficult (or even impossible) if some information is missing. The Committee warns against making diagnoses based on insufficient data, such as the result of a single laboratory test.

This is all the more applicable in cases where such tests are carried out in non-certified laboratories where it is often not clear whether the test has been conducted in accordance with a standardised procedure, whether valid tests have been used, and how and by whom the test results will be interpreted and announced.

It is of the utmost importance that the result be viewed in the context of the patient's disease history and of their complete clinical presentation. Conversely, if the attending physician provides the clinical microbiologist with full details of the patient's clinical complaints, this will help to ensure that the correct laboratory tests are used.. Input from this interview is also important when interpreting the results of such tests.

Alternative approach in the event of an indeterminate result

Despite the physicians' and patients' best efforts, the possibility cannot be excluded that the diagnostic path will conclude without producing a clear result. This situation occurs more often in patients with a low a priori probability of Lyme disease, coupled with long-term uncharacteristic complaints. If the complaints persist and other disorders have been excluded, then the patient is said to be suffering from 'medically unexplained physical symptoms'(MUPS), and a different approach to the treatment is required. The Committee will revisit this issue in Chapter 7.

5.4 The perspectives of those affected

In this section, the Committee discusses the perspectives of those affected with regard to the subject of diagnosis, as these emerged from the focus groups in particular.

The importance of an effective, clear diagnosis was emphasised by all of the focus groups. There is a widely accepted view that the tests used in the Netherlands are not conclusive. They all too often involve uncertainties about the results and hence the diagnosis.

There are various minor differences between the groups questioned. The physicians say that serological assays can never be one hundred percent watertight, either in the case of Lyme disease or any other infectious diseases, and that false positive and false negative results just tend to occur from time to time. Nevertheless, they do have a clear need for tests that can distinguish between an active infection and a past infection. They also need to understand the validity of tests used outside the regular Dutch healthcare system, such as the lymphocyte transformation test, PCR and bioresonance.

Patients are more critical of currently available laboratory tests. The parents of children with Lyme disease and patients with long-term complaints, in particular, state that the tests used in the Netherlands are inadequate. They claim that these tests too often fail to provide firm results, or that they give false negative results. Patient groups indicate that they need improved test methods and a more open attitude to the tests used abroad.

Another issue reported by patients is that physicians often fail to diagnose Lyme disease, for instance, by not recognising *erythema migrans* for what it is. Some GPs confirm that they have not always successfully recognised cases of EM.

5.5 Conclusion

A diagnosis of Lyme disease is made based on a carefully compiled case history and a physical examination, supported, in many cases, by laboratory tests. Serological assays are the preferred option here. The Committee feels that laboratory testing for Lyme disease should be performed using clinically validated tests, in accredited diagnostic laboratories.

The Committee also considers it important that the existing variation in serological assays used in the Netherlands should be reduced, and urges the swift and mandatory standardisation of such tests.

According to some scientific studies, many other laboratory techniques that are used from time to time can neither be standardised nor reproduced. For this reason, the Committee advises against the use of such tests. With regard to tests that have not yet been thoroughly investigated, it recommends that further research be carried out. A laboratory test capable of distinguishing between an active infection and a past infection would be a great asset indeed. The Committee recommends that priority be given to research into the development and validation of such tests.

Chapter 6

Antibiotic therapy

As it is caused by a bacterium, Lyme disease can, in theory, be treated with antibiotics. However, the treatment of Lyme disease can pose difficulties that are not usually encountered with other infectious diseases. Accordingly, in this chapter, the Committee addresses the topic of antibiotic therapy per individual patient group. In the vast majority of cases, patients who have received antibiotic therapy make a full and complete recovery. In some patients, however, the complaints persist, and this has given rise to a debate about the relative merits of extending this therapy. This aspect, too, has been examined by the Committee.

6.1 Differentiated approach

Lyme disease patients can present with a wide variety of disease symptoms, so diagnosis can take place at different stages in the disease process and the results of such diagnostic testing can also vary. Thus a careful consideration of the treatment options is of great importance.

In addition, there are patients in whom a diagnosis of Lyme disease cannot be confirmed, but who nevertheless identify this as the cause of their disease symptoms. The more persistent clinical pictures are often referred to as “chronic Lyme disease”. As indicated in Chapter 1, the use of this term has generated considerable debate.[33,51,57] The Committee cannot endorse the use of this term, as it feels that this unjustifiably classifies very different patients into a single group. Similarly, the Committee considers use of the term “post-Lyme syndrome” to describe uncharacteristic complaints following antibiotic therapy to be unhelpful. This is because complaints of this kind can also occur following other infections (e.g. mononucleosis or toxoplasmosis) or even in patients who have had no infection at all (or who were unaware of having had one). In such cases the mechanisms which give rise to these complaints are unknown.[58]

To properly reflect patient diversity and to deliver a well-considered advisory report, when interviewing patients about antibiotic therapy, the Committee classified them on the basis of disease symptoms (characteristic symptoms or uncharacteristic complaints), previous antibiotic therapy, and – in some groups – the results of the serological assay. It based this approach on the ones described in various publications.[18,59]

Using this approach, the Committee has defined the following six categories of patients:

1. patients with the characteristic symptoms of early localised Lyme disease and early disseminated Lyme disease who have not previously received antibiotic therapy (*early-stage Lyme disease*)
2. patients with the characteristic symptoms of late-stage Lyme disease who have not previously received antibiotic therapy (*late-stage Lyme disease*)
3. patients with characteristic symptoms (which may be persistent), who have previously received antibiotic therapy (*possibly persistent Lyme disease, reinfection or residual damage*)
4. patients with uncharacteristic (long-term) complaints, who have previously received antibiotic therapy
5. patients with uncharacteristic (long-term) complaints, who have not previously received antibiotic therapy and who have positive serological assay results
6. patients with uncharacteristic (long-term) complaints, who have not previously received antibiotic therapy and who have negative serological assay results.

In the following sections, the Committee discusses treatment approaches for the various groups of patients. In this context, the Committee points out that the decision on whether or not to treat individual patients, naturally, remains the responsibility of the attending physician, in consultation with the patient.

6.2 The treatment of patients with characteristic symptoms

Patients with the characteristic symptoms of early localised Lyme disease and early disseminated Lyme disease who have not previously received antibiotic therapy

In this category of patients, antibiotic therapy is indicated, for a period of ten days in patients with EM, for example. For a specific description of the treatment, the Committee refers the reader to the Dutch Institute for Healthcare Improvement's guideline on Lyme disease.[37]

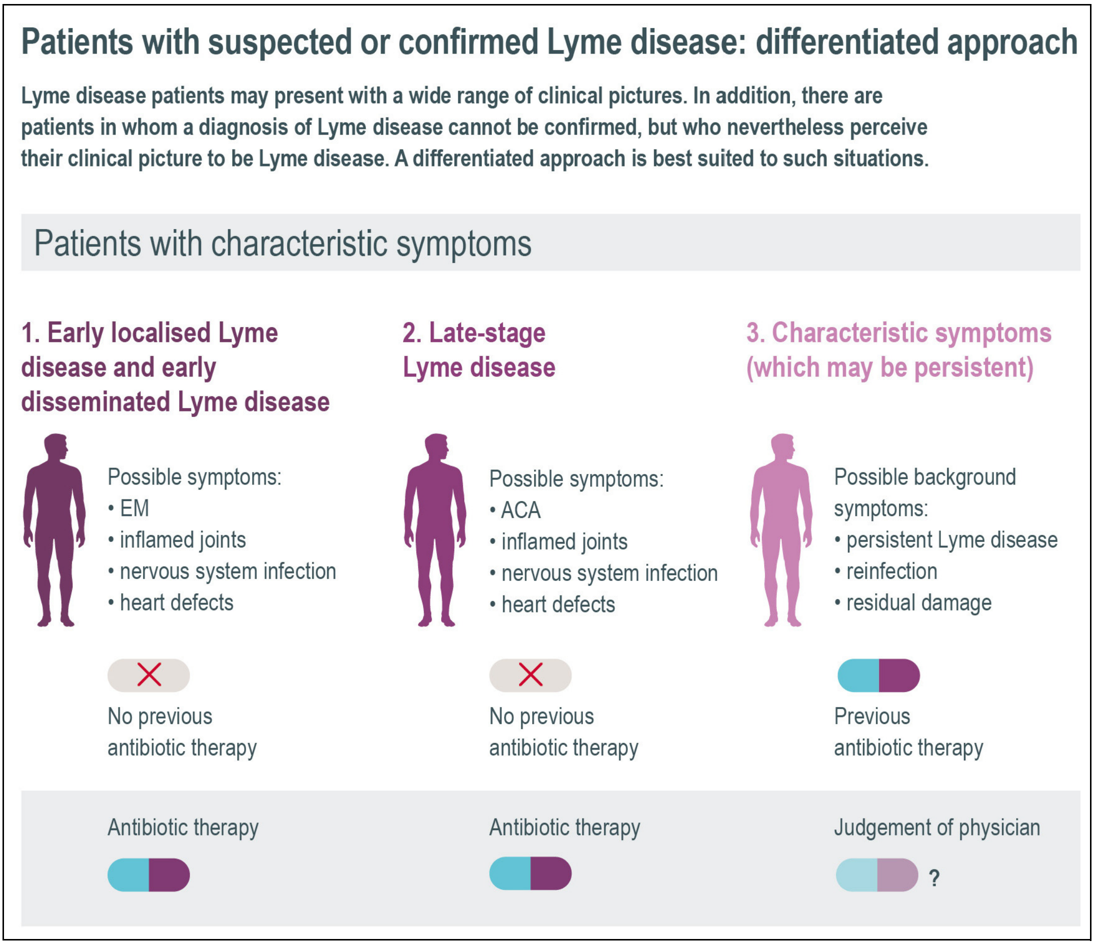
Patients with the characteristic symptoms of late-stage Lyme disease who have not previously received antibiotic therapy

In this category of patients, antibiotic therapy is indicated. Depending on how the disease manifests itself, it may be necessary either to extend the treatment or to switch to another type of antibiotic. In the case of patients with arthritis, for example, an extension of up to thirty days may be required. For a specific description of the treatment, the Committee refers the reader to the Dutch Institute for Healthcare Improvement's guideline on Lyme disease.[37]

Patients with characteristic symptoms (which may be persistent), who have previously received antibiotic therapy

Some patients who have previously completed a course of antibiotic therapy may still suffer from characteristic symptoms. This could indicate either residual damage (the Committee will revisit this issue in the following chapter), persistence of the original disease, or a new manifestation of the disease. With regard to cases involving a manifestation of EM following a previous course of treatment and following a prolonged complaint-free period, a recently published study indicates that, in all of the cases examined, this was caused by infection with a new type of Lyme bacterium to which the patient had not been previously exposed, rather than to persistence of the initial bacterium.[60] It should be noted that this has no bearing on the treatment options. Whether persistence or reinfection is involved, additional antibiotic therapy is indicated in both cases. For a specific description of the treatment, the Committee refers the reader to the Dutch Institute for Healthcare Improvement's guideline on Lyme disease.[37]

In summary, the recommended treatment for this group of patients is as follows:



Patients with suspected or confirmed Lyme disease: differentiated approach

Lyme disease patients may present with a wide range of clinical pictures. In addition, there are patients in whom a diagnosis of Lyme disease cannot be confirmed, but who nevertheless perceive their clinical picture to be Lyme disease. A differentiated approach is best suited to such situations.

Patients with characteristic symptoms

1. Early localised Lyme disease and early disseminated Lyme disease

Possible symptoms:
- EM
- inflamed joints
- nervous system infection
- heart defects

✗ No previous antibiotic therapy

Antibiotic therapy

2. Late-stage Lyme disease

Possible symptoms:
- ACA
- inflamed joints
- nervous system infection
- heart defects

✗ No previous antibiotic therapy

Antibiotic therapy

3. Characteristic symptoms (which may be persistent)

Possible background symptoms:
- persistent Lyme disease
- reinfection
- residual damage

Previous antibiotic therapy

Judgement of physician

?

Figure 3a Patients with suspected or confirmed Lyme disease: differentiated approach.
Patients with characteristic symptoms.

6.3 The treatment of patients with uncharacteristic complaints

Patients with uncharacteristic (long-term) complaints, who have previously received antibiotic therapy

Some Lyme disease patients who have previously completed a course of antibiotic therapy may still suffer from long-term uncharacteristic complaints. Attending physicians should assess whether their patient still has an on-going infection with the Lyme bacterium. Based on this assessment, they can then decide whether or not to prescribe a further course of antibiotic therapy for the patient in question. If the physician feels that the patient may still have an infection, further antibiotic therapy will be administered. If an infection is considered to be unlikely, however, the Committee advises against the use of antibiotic therapy. Instead, consideration should be given to other ways of treating the patient. The Committee will revisit this issue in the next chapter.

Patients with uncharacteristic (long-term) complaints, who have not previously received antibiotic therapy and who have positive serological assay results

If patients present with purely uncharacteristic complaints, then a diagnosis of Lyme disease cannot be made. The Committee has previously stated that these uncharacteristic complaints can be caused by a range of diseases. In some cases, the basis of these complaints is unknown. While the presence of antibodies to the Lyme bacterium does indicate that a patient has been in contact with this organism, this is not the same thing as having an actual infection at that point in time. After all, up to ten percent of the healthy population has antibodies against the Lyme bacterium.[51,52]

In a patient with uncharacteristic complaints and positive serological assay results for Lyme disease, the attending physician must estimate (on the basis of the subject's case history) the probability that the individual in question has a developing (or active) infection at that point in time. For instance, if there is a clear time relationship to the occurrence of a tick bite, the decision may be taken to initiate antibiotic therapy.[59] If an infection is considered to be unlikely, however, the Committee advises against the use of antibiotic therapy. Instead, an attempt should be made to find other treatment options.

Patients with uncharacteristic (long-term) complaints, who have not previously received antibiotic therapy and who have negative serological assay results.

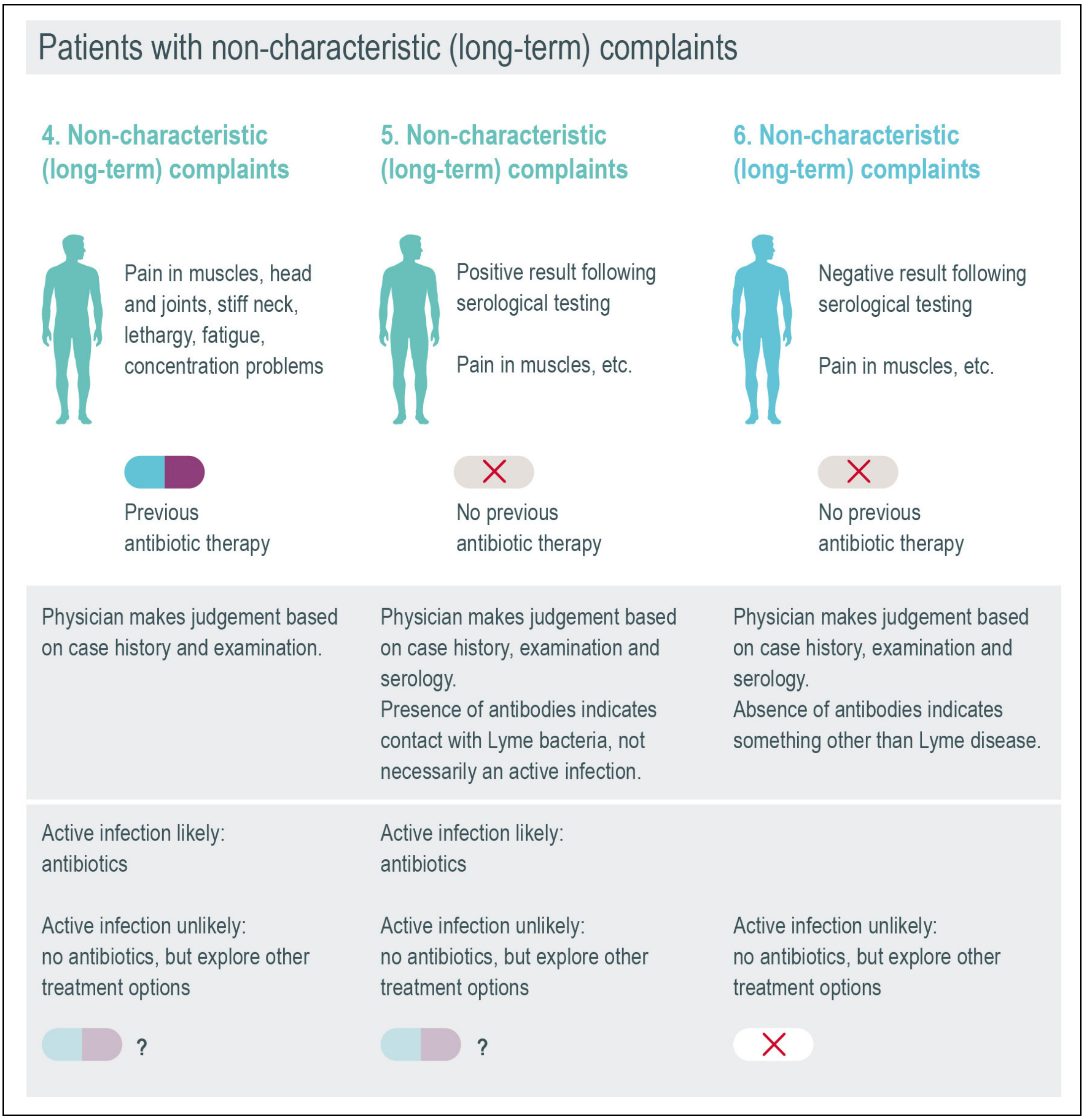
In individuals with uncharacteristic complaints (for Lyme disease), a case history, and a physical examination that do not indicate Lyme disease, as well as negative serological assay results for Lyme disease, the Committee takes the view that there is no evidence to suggest that such patients are actually suffering from Lyme disease. The combination of case history, clinical details, and the results of serological assays indicates that an active infection is highly unlikely.[37] The Committee is, therefore, of the opinion that antibiotic therapy should not be used. Treatment recommendations for the second group of patients are shown in Figure 3b.

6.4 Results of short-term use of antibiotics

After ten days of antibiotic therapy, the prognosis for Lyme disease (especially in its early stages) is generally good, although it may be a lengthy period of time before the patient makes a full and complete recovery. For instance, six months after being treated for early-stage Lyme disease, eleven percent of patients are still suffering from uncharacteristic complaints. Later in the post-treatment period this figure drops to five percent. Six to seventeen percent of patients treated for arthritis resulting from Lyme disease suffer from persistent complaints. It is not clear from these figures how many cases involve complaints resulting from residual damage and how many are due to persistent infections. One year after being treated for neuroborreliosis, a significant proportion of patients are still suffering from uncharacteristic complaints (12 to 33 percent) or residual damage in the form of neuropathy, paresis and sensory disorders (9 to 27 percent).[37]

6.5 Results of longer-term use of antibiotics

Complaints that persist for lengthy periods of time may give rise to a suspicion that antibiotic therapy has failed and that the Lyme bacterium is persisting in the patient’s body. This suspicion has led to patients being given long-term antibiotic therapy, in some cases for many years. This issue has generated considerable debate.



Patients with non-characteristic (long-term) complaints

4. Non-characteristic (long-term) complaints	5. Non-characteristic (long-term) complaints	6. Non-characteristic (long-term) complaints
Pain in muscles, head and joints, stiff neck, lethargy, fatigue, concentration problems	Positive result following serological testing Pain in muscles, etc.	Negative result following serological testing Pain in muscles, etc.
Previous antibiotic therapy	✗ No previous antibiotic therapy	✗ No previous antibiotic therapy
Physician makes judgement based on case history and examination.	Physician makes judgement based on case history, examination and serology. Presence of antibodies indicates contact with Lyme bacteria, not necessarily an active infection.	Physician makes judgement based on case history, examination and serology. Absence of antibodies indicates something other than Lyme disease.
Active infection likely: antibiotics Active infection unlikely: no antibiotics, but explore other treatment options ?	Active infection likely: antibiotics Active infection unlikely: no antibiotics, but explore other treatment options ?	Active infection unlikely: no antibiotics, but explore other treatment options ✗

Figure 3b Patients with suspected or confirmed Lyme disease: differentiated approach. Patients with uncharacteristic (long-term) complaints.

Accordingly, the Committee has discussed the results of published studies in this area. In this context, it includes the Dutch Cochrane Centre analysis, carried out at the instigation of the Health Council, of the effectiveness of long-term antibiotic therapy for Lyme disease, and any associated adverse effects.[61] The report of this analysis has been included in the background studies to this advisory report. These details can be found at the Health Council website.

Published studies

The DCC reviewed 17 publications on studies into the effects of prolonged antibiotic therapy in Lyme disease patients. These studies exhibit considerable variation, not only regarding the included patients, study design and implementation, but also in terms of quality.

Eleven of these published articles involved randomised controlled trials (RCTs), in which different groups of patients are compared to one another. The other publications involved observational studies, in which groups of patients were monitored for specific periods of time. Greater value is attached to the results of RCTs than to those obtained in observational studies.

Treatment results

Only one RCT compared two groups of patients who had been treated with the same antibiotic for different periods of time.[62] The study in question involved patients with late disseminated Lyme disease. The outcome of a 28-day period of therapy with ceftriaxone was no better than that obtained following treatment with the same agent for 14 days.[62]

The other RCTs were much less suitable for direct comparisons of the effects of short-term and long-term antibiotic therapy. For instance, while two RCTs of antibiotic therapy in EM patients tested a range of antibiotics, they did not vary the period of treatment involved.[63,64] Two other RCTs tested different antibiotics with varying periods of therapy in patients with EM[65] and patients with late disseminated Lyme disease.[66] Five RCTs compared antibiotic therapy to the effect of a placebo in patients with early disseminated Lyme disease[67] and in patients with persistent uncharacteristic complaints following initial antibiotic therapy[68-72]. One of these RCTs produced two publications.[68,69] The longest period of therapy studied was 100 days.[67]

The DCC concludes that no evidence has emerged from this research to indicate that prolonged antibiotic therapy is more effective than the standard treatment.[61] According to the DCC, limitations inherent to the RCTs in question mean that the minor differences found between antibiotic therapy and the use of a placebo cannot simply be generalised. The DCC states that the published observational studies do not allow any definite conclusions to be drawn. This is not only due to the lack of control groups, but also to differences in experimental design and, in some cases, to poor quality.[61] The Committee endorses this standpoint. The DCC concludes that none of the published literature meets the most demanding criteria in terms of experimental rigour. There is a general lack of good-quality randomised clinical trials.

The DCC expresses the view that, based on the available scientific literature, the possibility of an effect resulting from prolonged antibiotic therapy cannot be excluded. The Committee concurs with this view. It therefore recommends that research (in the form of an RCT) be carried out into the effectiveness of prolonged antibiotic therapy in patients with Lyme disease. In this connection, the Committee suggests that the period of therapy involved be limited to 12 weeks. If antibiotic therapy fails to produce any results within that time, a more prolonged period would be unlikely to be successful.

The Committee is cognisant of the fact that, in other cases, there are good reasons for favouring long-term antibiotic therapy. As examples, it cites the treatment of tuberculosis, of chronic Q fever or of an infected heart valve prosthesis. In general, such therapy leads to a clear-cut and rapid improvement in the patient's complaints, coupled with a decrease in the inflammatory response. The purpose of extending this therapy for a more protracted period is to prevent the recurrence of symptoms.

Results concerning adverse effects

As with any medicinal product, the use of antibiotics can involve adverse effects. The five above-mentioned RCTs are particularly important as they analyse the occurrence of adverse effects, comparing antibiotic therapy with a placebo.[67-72] Further details can be obtained from the RCT in which the same antibiotic was used for varying periods of time.[62]

Serious adverse effects were rare, also they occurred no more often in the antibiotic group than in the placebo group. Klempner et al described the occurrence of two serious adverse effects in the antibiotic group, but none in the placebo group. Krupp et al reported a single serious adverse effect in the antibiotic group and three in the placebo group.[68,70]

Mild adverse effects, such as diarrhoea, are far more common, affecting a quarter to half of all patients. In the study by Oksi et al, these mild adverse effects were found to be more common in the antibiotic group than in the placebo

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group.[67] In terms of adverse effects, the other studies either revealed no difference between the antibiotic group and the placebo group, or they drew no conclusions regarding the statistical significance of any differences found. [68,70-72] In the study comparing two different treatment periods using the same antibiotic, the dropout due to adverse effects was greater after 28 days of treatment than after 14 days of treatment.[62]

6.6 The perspectives of those affected

In this section, the Committee discusses the perspectives of those affected with regard to the subject of treatment, as described by the focus groups in particular.

Treatment was discussed in all of the focus groups. Many early-stage Lyme disease patients report that they were only given five days of antibiotic therapy, yet the guideline stipulates a period of ten days.

However, the main point of concern in terms of treatment involves long-term complaints. Patients worry about chronic Lyme disease, expressing the view that a prolonged period of antibiotic therapy would be appropriate. Being denied such therapy in the Netherlands, they feel that they have no choice but to seek it abroad. Patients in search of a solution also report that they feel compelled to turn to alternative medicine.

The participating physicians, some of whom are GPs, claim that they routinely follow the guideline. Indeed, some specialists report that they sometimes prescribe prolonged periods of therapy. However, as they have to rely solely on case histories rather than on scientific evidence, this is not a frequent occurrence.

This suggests that it might be worthwhile to pursue research into the effectiveness of prolonged periods of therapy (several months), combinations of different antibiotics, and alternative treatments. Physicians would also like to see research carried out into the effect of cognitive behavioural therapy, possibly in combination with antibiotic therapy.

Another issue raised by patients is a perceived lack of follow-up. After completing their course of therapy, many of them still have questions about on-going complaints or about the therapy itself. None of the participating physicians cited follow-up as an issue of concern.

Finally, both patients and healthcare professionals point out that while there is a clear need for a multidisciplinary approach to Lyme disease, this is still the exception rather than the rule in everyday practice.

6.7 Conclusion

On the short-term use of antibiotics

In theory, Lyme disease responds well to antibiotic therapy. In some patients, however, the complaints persist or recur after antibiotic therapy, and this has prompted a debate about the relative merits of extending such therapy.

The Committee recommends that previously untreated patients with characteristic symptoms of early-stage or late-stage Lyme disease (who correspond to its definitions of groups 1 and 2) should receive antibiotic therapy in accordance with the applicable guideline. Aside from cases of residual damage, those patients with characteristic symptoms (which may be persistent) who have previously completed a course of antibiotic therapy (group 3) are probably suffering from persistence of the Lyme bacterium or from reinfection. In such cases, the Committee recommends the use of additional antibiotic therapy in accordance with the applicable guideline.

In treated patients with uncharacteristic (long-term) complaints; group 4) and in untreated patients with uncharacteristic complaints and positive serological assay results for Lyme disease (group 5), the Committee recommends that attending physicians estimate (on the basis of the subject's case history and a physical examination) the probability that the individual in question has an active infection, and on that basis decide whether or not to proceed with additional antibiotic therapy for the standard period of time.

In untreated patients with uncharacteristic complaints, a case history and a physical examination that do not point to Lyme disease, as well as negative serological assay results for Lyme disease (group 6), the Committee advises against the use of antibiotic therapy.

On the longer-term use of antibiotics

The Committee concludes that, given the current level of knowledge, too few research results support prescribing antibiotics to Lyme disease patients for more prolonged periods of time than those stipulated in the guideline, for instance ten days in the case of EM, to thirty days in the case of Lyme arthritis.

Treatment may be extended by another ten or thirty days if patients are still suffering from characteristic symptoms that their attending physicians feel are the result of an on-going active infection.

In the event of residual damage or purely uncharacteristic complaints, extending the therapy will serve no useful purpose. Accordingly, the Committee advises against this course of action.

On further research

Published studies vary considerably in terms of their design and implementation, and some are of relatively poor quality. In the Committee's view, it is extremely important that methodologically adequate research be conducted into prolonged antibiotic therapy for Lyme disease patients.

An RCT into prolonged therapy is currently taking place in the Netherlands. The results are expected to be published in late 2014.[73] At that time, the results of this study should be analysed to determine whether they give sufficient grounds for amending the Committee’s treatment recommendations.

A new point of special interest, which was raised during the focus group survey, is the need for follow-up following treatment for Lyme disease.

Chapter 7

If antibiotic therapy is not indicated

In the previous chapter, the Committee identified those types of Lyme disease patients to whom, in its view, antibiotic therapy should be given. The Committee also identified those patients for whom such treatment is not indicated. According to the Committee, the latter group includes patients in whom active Lyme disease cannot be confirmed (or can no longer be confirmed). However, even if antibiotic therapy is not indicated, the patient's complaints should still be taken seriously. Physicians and patients must work together to find potential solutions. Accordingly, this chapter addresses complementary treatments that might benefit patients with long-term disease symptoms.

7.1 Differentiated approach

When antibiotic therapy is not indicated, this does not mean that physicians have nothing more to offer to patients who are suffering from complaints. To this end, it is again advisable to adopt a differentiated approach, as patients can present with a range of different clinical pictures.

For instance, the patients involved may have residual symptoms from a previous bout of Lyme disease, such as nerve damage or persistent or recurrent arthritis. There are also patients who are slowly recovering from uncharacteristic complaints, such as fatigue following antibiotic therapy. Other patients experienced complaints that appeared to be unrelated to Lyme disease (treated or otherwise).

If no adequate physical explanation can be found for the complaints experienced by patients then these are classified – by definition – as “medically unexplained physical symptoms” (MUPS). MUPS is a term that covers a wide range of complaints. This is evident from the definition used in the Netherlands: “We use the term Medically Unexplained Physical Symptoms (MUPS) to describe physical complaints that persist for more than a few weeks and for which, following proper medical examination, no medical condition can be found that can adequately account for the complaint in question.”[74] At one end of the spectrum is a single unexplained physical complaint while at the other extreme there are protracted and persistent complex combinations of complaints that can have a major impact on people’s ability to perform their everyday activities.[74] MUPS involves various interrelated patterns of complaints for which no disease-specific abnormalities of structure or function can be identified.[75] The names given to these patterns of complaints usually reflect the specialism of the physician treating the patient in question. Some examples are fibromyalgia (rheumatology) and chronic fatigue syndrome (internal medicine).

7.2 Treatment options

In recent years, the treatment of patients with residual damage or uncharacteristic (long-term) complaints has increasingly focused on an integrated approach, rather than on purely physically-based or mentally-based approaches.[76]

Symptomatic treatment

All that some of these patients may need is a pragmatic approach to treatment, one that involves seeking ways to alleviate their symptoms. Accordingly, the Committee recommends that complaints caused by residual damage be symptomatically treated by physiotherapy, for example, or by prescribing anti-inflammatory drugs.[77-79]

Complaint-centred therapy

If patients continue to experience difficulties in the performance of their everyday activities then a complaint-centred therapy may be indicated, one that focuses on ways of dealing with these obstacles. This therapeutic approach can take one of several different forms. However, the Committee limited its discussion to cognitive behavioural therapy (CBT), as this has been much more widely used than other therapies.

CBT aims to change patients' cognitions and behaviours, thus enabling them to gain control over their complaints.[58,75,80] CBT appears to be effective in the treatment of somatic disorders such as rheumatoid arthritis and muscle diseases, but it is also used in various groups of patients with unexplained complaints such as persistent fatigue after cancer or chronic fatigue syndrome.[58,81,82] A substantial proportion of patients in the latter group go on to make a full and complete recovery.

While there is sometimes a considerable degree of overlap in the complaint patterns exhibited by the various groups of patients who may benefit from CBT, the variation in their backgrounds necessitates specific adaptations to the type of cognitive behavioural therapy provided. This involves examining each patient or patient group for factors that may be precipitating or perpetuating the complaints in question. In its advisory report on chronic fatigue syndrome, the Health Council described the PPP model, one of the approaches used to tackle this condition.[58] The three Ps in the PPP model stand for predisposing, precipitating and perpetuating.[83]

The authors of the MUPS guideline recommend that this should be supplemented by Engel's biopsychosocial model.[74] Combining the two models creates a matrix that can be used to identify the biological, psychological and social factors that affect the development and course of the disease symptoms. For the purposes of illustration, in the summary below the Committee lists factors that could be involved in cancer fatigue.

This model enables physicians and patients to discuss various factors that might have precipitated the complaints, such as Lyme disease. In their discussions, physicians and patients can also consider what factors might be perpetuating the complaints. As biological, psychological and social factors are all interlinked, treatment focusing on any one of these factors may also produce improvement in the others.

	Predisposing	Provocative	Perpetuating
Biological	Biological vulnerability	Cancer	Physical deconditioning
Psychological	Personality	Cancer (and the related stress and worry about illness and death)	Fear of cancer recurrence
Social	Profound experiences with cancer among immediate family and friends	Cancer (and the shock affecting others in the patient's social environment)	Lack of support after being cured of cancer

The Committee is unaware of any research into the effect of CBT in patients suffering from long-term complaints after a bout of Lyme disease or in patients whose complaints are attributed to Lyme disease. There is a need for research into the effectiveness of CBT in these patients.

7.3 The importance of a good treatment relationship

In the case of residual damage and persistent complaints, as with other disorders, it is important for physicians to encourage their patients to take an active part in dealing with the complaints. This is called patient empowerment.[84] At the same time, it is important that physicians be alert to the vulnerable position in which their patients find themselves. A good doctor-patient relationship is essential for a favourable outcome. Much more progress needs to be made in this area, in terms of trust and constructive cooperation.[84]

7.4 The perspectives of those affected

In this section, the Committee discusses the perspectives of those affected with regard to treatment, if antibiotics are not indicated, as described by the focus groups in particular.

Patients feel that Lyme disease requires a multidisciplinary approach. This certainly also applies to the patients discussed in this chapter: those with persistent complaints or residual damage following treatment for Lyme disease.

Patients cite examples of physicians who failed to take them seriously and referred them to a psychologist or psychiatrist, believing that their problem was “all in the mind”. For this reason, the patients are suspicious of additional treatment options, such as cognitive behavioural therapy.

In interviews with physicians, it emerged that explaining the need to involve a psychologist in the treatment poses no difficulty, provided that sufficient time is allowed for this and if it is presented as a supplementary therapy in the context of an integrated approach.

Patients with long-term complaints indicate that they feel compelled to turn to alternative medicine for a solution, but they also say that effective follow-up might alleviate much of their doubt and agitation.

7.5 Conclusion

Treating Lyme disease patients with antibiotics does not always eradicate their complaints quickly, and in some cases not at all. Persistent uncharacteristic complaints may have a somatic cause, but they could also be related to psychological and social factors.

If no adequate somatic explanation can be found for long-term complaints then these are classified – by definition – as “medically unexplained physical symptoms”. It is not clear whether, following a bout of acute Lyme disease, patients have a greater chance of developing long-term complaints nor, if this is indeed the case, which patients might be affected.

The Committee feels that a recognition of such patients’ health problems and associated issues should form the basis for working partnerships between physicians and patients, aimed at finding potential solutions.

In medicine, the treatment of patients with long-term complaints has increasing focused on an integrated approach, rather than on purely physically-based or mentally-based approaches. The Committee recommends that the former approach should also be adopted in patients suffering from long-term complaints after a bout of Lyme disease or in patients whose complaints are attributed to Lyme disease.

Complaints caused by residual damage can be symptomatically treated by physiotherapy, for example, or by prescribing anti-inflammatory drugs. Cognitive behavioural therapy often forms part of an integrated approach to the treatment of patients with long-term complaints. CBT aims to change patients’ cognitions and behaviours, thus enabling them to gain control over their complaints. The therapy has been found to be effective in patients suffering from chronic fatigue syndrome and rheumatoid arthritis. Patients indicate that effective follow-up might alleviate much of their agitation.

The Committee recommends that research be carried out into the effectiveness of CBT in patients suffering from long-term complaints after a bout of Lyme disease or whose complaints are attributed to Lyme disease.

Chapter

8

The provision of information, expertise and training

The Citizens' Initiative includes two points relating to the expertise and training of physicians, and to the provision of information to the general public. The Committee's remit was to make recommendations concerning the diagnosis and treatment of Lyme disease, and to identify any under-researched areas. Accordingly, the focus group survey was primarily designed with that in mind. However, a point of special interest cited by all focus groups concerned a lack of emphasis on the issue of prevention, which was reflected by inadequate information provision and by a poor grasp of the essentials of Lyme disease among physicians. For that reason, the Committee has devoted a separate chapter to this topic.

8.1 Provision of information and prevention

Prevention was identified as a point of major concern by each of the focus groups. Patients and the parents of children with Lyme disease point to a lack of individual and collective preventive measures. They cite the cause as a deficit of actively supplied, reliable information (provided by the government or by other bodies), and they feel that there is a need for a national information centre. After all, the information available on the internet is very varied and contradictory. Patients and parents are also unhappy that they are compelled to search for information themselves, rather than having it actively offered to them.

Those who engage in recreational activities that involve a high risk in this regard point out that in nature reserves abroad it is much more common to see signs warning hikers about the dangers posed by ticks. These signs also show people how to check themselves for the presence of ticks and how to remove them.

Those professional groups with an increased risk of tick bites and Lyme disease point out that their employers and occupational physicians are not sufficiently well informed about the risk of tick bites, about Lyme disease, and about preventive measures. They take the view that Lyme disease should be classified as an occupational disease.

The Committee has also found that the provision of information on the internet is far from ideal. There is a lot of conflicting information. It is not clear to the general public which sources are reliable and which are not, nor where they can find the best information. For instance, the National Institute of Public Health and the Environment (RIVM) website is not at the top of the hit list generated by entering “Lyme disease” into the Google search engine.* Accordingly, the Committee welcomes the various initiatives undertaken by RIVM to improve the provision of information about Lyme disease, which involves a pivotal role for the organisation’s website.[85]

8.2 How well informed are physicians?

Knowledge, or a lack thereof, was a very common theme among the focus groups.

Patients assert that many GPs and specialists have only a patchy knowledge of Lyme disease. In their view, physicians are poorly informed about the occurrence of Lyme disease in their area, and they often fail to recognise an EM for what it is. Moreover, specialists tend not to consider Lyme disease in patients presenting with joint or neurological complaints, nor are they sufficiently well informed about diagnosis and treatment.

The GPs and specialists contend that there are gaps in our scientific understanding of the pathogenesis, diagnosis (there is no test that can distinguish between a past infection and an active infection) and treatment of persistent complaints. Some GPs also admit that they sometimes feel that their knowledge is not all that it could be, in terms of diagnosis (case history, physical examination and laboratory tests) or treatment.

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* https://www.google.nl/search?q=ziekte+van+lyme&ie=utf-8&oe=utf-8&aq=t&rls=org.mozilla:nl:official&client=firefox-a, last checked on 15-05-2013.

Physicians take the view that knowledge gleaned by patients from foreign sources is not always particularly useful, due to a lack of clarity concerning its origin or scientific reliability.

8.3 Quality of the treatment relationship

In line with concerns about the extent of physicians' familiarity with Lyme disease, in the focus groups the patients and parents of children with this disease cited treatment by physicians as a major point of concern. Patients are sent home having been told that they do not have (or could not possibly have) Lyme disease, and no action is taken with regard to their existing complaints.

For their part, the participating physicians are sometimes upset by the way they are treated by some patients when their findings do not match these individuals' preconceived views on the matter. The physicians also find it difficult to assess the value of the copious quantities of information that are sometimes supplied by patients. It is sometimes difficult to determine which information is scientifically based and which is not. This hampers doctor-patient communication.

The Committee has identified the above-mentioned treatment issues as a point of concern.

8.4 Variation in expertise and approach

In the Netherlands, physicians treating Lyme disease patients exhibit a degree of variation in their expertise and approach. Physicians in primary and secondary healthcare sometimes feel ill-equipped to treat (or meet the requirements of) Lyme disease patients (especially those with late-stage Lyme disease) or patients who attribute their complaints to Lyme disease. In addition, the more highly specialised treatment centres in secondary and tertiary healthcare each take a different approach. Psychological expertise is one aspect that is often missing from the treatment of complaints that can occur during a bout of Lyme disease, or thereafter.

8.5 Conclusion

The Committee recognises the following points of concern in the areas of knowledge and information provision. The body of scientific knowledge about Lyme disease is incomplete, the information available on the internet is very variable in terms of quality and is sometimes contradictory, and the results of scientific studies are not always clear.

The Committee is concerned about the identified lack of knowledge regarding Lyme disease (which has been recognised by a number of GPs), which cannot be entirely ascribed to shortcomings in the scientific knowledge on this topic. In addition, there is considerable variation in physicians' expertise regarding Lyme disease, and in the approach they take.

This situation could be improved by a greater focus on this issue during medical training programmes and in physicians' professional development programmes. The provision of information could also be better. The implementation of these steps would probably also help to alleviate the perceived treatment issues. This is supported by statements by focus group survey participants, indicating that they expected improvements in the provision of information to relieve some of the pressure on the doctor-patient relationship that results from differences of opinion regarding the causes of the complaints. Be that as it may, the issue of how to improve the treatment process for both parties involved merits consideration.

Chapter 9

Conclusions and recommendations

This chapter is a compilation of the Committee’s conclusions and recommendations regarding the diagnosis and treatment of Lyme disease. It also includes various recommendations on the development and compilation of knowledge and expertise, and on the provision of information. Each of these are areas where gains can still be made. The Committee also recommends ways of closing the identified knowledge gaps.

9.1 The importance of common viewpoints

When it is recognised at an early stage, Lyme disease can often be effectively treated with antibiotics. In the event of persistent symptoms or uncharacteristic complaints, the picture becomes more complex and both patients and physicians are occasionally affected by increasing uncertainty. This uncertainty may then, in turn, cause some awkwardness in the consulting room, with both parties being keenly aware of a lack of common viewpoints.

It is the Committee’s hope that its recommendations in this final chapter and its advice concerning treatment for the six groups of patients will help to create a clearer and more consistent line in the diagnosis and treatment of Lyme disease. This should provide greater certainty while, at the same time, leading to a proliferation of generally accepted viewpoints.

However, it will not be possible to achieve absolute certainty for everyone. For this reason, the advisory process made specific allowance for the difficulties encountered by patients who, after being treated for Lyme disease, continue to suffer from persistent, unexplained complaints. Consideration should also be given to cases in which long-term complaints cannot be associated with Lyme disease and physicians are unable to offer an alternative explanation.

Dealing with such uncertainty is one of the most difficult challenges facing patients and physicians. Every effort must then be made to determine what constitutes good care in that particular situation. Further improvements in diagnosis will leave less room for doubt, thereby facilitating the development of constructive partnerships between patients and physicians. Yet, in the absence of an explanation, it also requires a willingness by both sides to engage in a discussion about what constitutes the best form of care.

9.2 Improving the diagnosis

A diagnosis of Lyme disease is made based on a carefully compiled case history and a physical examination, supported, in many cases, by laboratory tests. One problem is that the best currently available laboratory technique is an indirect test method. Rather than detecting the Lyme bacterium itself, it focuses on antibody generation (a bodily response to the bacterium). The Committee has formulated the following recommendations:

- It is best to consider the a priori probability of Lyme disease when deciding whether or not to have additional tests (including laboratory tests) carried out.
- Laboratory testing for Lyme disease should be performed using clinically validated tests, in accredited diagnostic laboratories.
- A range of serological tests are used in the Netherlands, many of which have been validated but not standardised. This means that tests on the blood of a Lyme disease patient (especially one with early-stage Lyme disease) can produce a negative test result in one laboratory and a positive test result in another. Accordingly, the Committee urges the swift and mandatory standardisation of tests used in the Netherlands.
- A laboratory test capable of distinguishing between an active Lyme bacterium infection and a past infection would be a great asset indeed. The Committee recommends that priority be given to research into the development and validation of such tests.

9.3 Improving treatment

Treating Lyme disease patients with antibiotics

Lyme disease is an infectious bacterial disease that, in theory, responds well to antibiotic therapy. In some patients, however, the complaints persist or recur, and this has prompted a debate about the relative merits of extending such therapy. In this connection, the Committee has formulated recommendations that are based on the current level of knowledge. However, it emphasises that the decision on whether or not to proceed with treatment is the responsibility of the attending physician, in consultation with the patient.

In the Committee's view, previously untreated patients with characteristic symptoms of early-stage or late-stage Lyme disease should receive antibiotic therapy in accordance with the applicable guideline. Aside from cases of residual damage, the Committee recommends that patients with characteristic symptoms (persistent or otherwise) who have previously completed a course of antibiotic therapy should receive additional antibiotic therapy, in accordance with the applicable guideline.

In patients with uncharacteristic (long-term) complaints who have previously completed a course of antibiotic therapy, the Committee recommends that attending physicians estimate (on the basis of the subject's case history and a physical examination) the probability that the individual in question has an active infection, and on that basis decide whether or not to proceed with additional antibiotic therapy for the standard period of time. The same approach is indicated in the case of patients with uncharacteristic complaints who have not previously completed a course of antibiotic therapy and who have positive serological assay results for Lyme disease.

In untreated patients with uncharacteristic complaints, a case history and a physical examination that do not point to Lyme disease, as well as negative serological assay results for Lyme disease, the Committee advises against the use of antibiotic therapy.

The Committee notes that very few research results support the merits of giving Lyme disease patients antibiotic therapy for more than four weeks, unless there is clear evidence of a persistent infection. For this reason, the Committee advises against the use of prolonged therapy at the present time. In this context, the Committee notes that published studies vary considerably in terms of their design and implementation, and some are of relatively poor quality. Accordingly, further research is required. While this advisory report was being prepared, a study was under way in the Netherlands into prolonged antibiotic therapy in patients who had previously had Lyme disease and who were suffering from long-term uncharacteristic complaints.[73] The results of this study will probably be published in late 2014. The Committee has formulated the following recommendation:

- When the results of the study currently under way in the Netherlands are published, the Committee recommends that these should be analysed to determine whether they give sufficient grounds for amending its treatment recommendations and whether further research (in the form of RCTs) into protracted treatment is required.

The treatment of patients with residual damage or uncharacteristic (long-term) complaints

Treating Lyme disease patients with antibiotics does not always eradicate their disease symptoms quickly, and in some cases not at all. These sometimes persist, due to residual damage to nerves and joints, for example. In some cases, uncharacteristic complaints can persist for lengthy periods of time. In addition to somatic factors, the development of such complaints might also involve psychological and social factors.

If no adequate somatic explanation can be found for these persistent complaints then these are classified – by definition – as “medically unexplained physical symptoms”. It is not clear whether, following a bout of acute Lyme disease, patients have a greater chance of developing long-term complaints nor, if this is indeed the case, which of these individuals might be affected.

The Committee has formulated the following recommendation for this group of patients:

- It is important that the patient’s complaints be taken seriously. Physicians and patients must work together to find potential solutions.
- Complaints caused by residual damage can be symptomatically treated by physiotherapy, for example, or by prescribing anti-inflammatory drugs.
- In medicine, the treatment of patients with residual damage or persistent uncharacteristic complaints has increasingly focused on an integrated approach, rather than on purely physically-based or mentally-based approaches. The former approach is also recommended for patients suffering from persistent disease symptoms after a bout of Lyme disease or whose complaints are attributed to Lyme disease.
- Complaint-centred therapy, such as cognitive behavioural therapy, often forms part of an integrated approach to the treatment of patients with

persistent complaints. CBT aims to change patients' cognitions and behaviours, thus enabling them to gain control over their complaints. The therapy has been found to be effective in patients suffering from rheumatoid arthritis, muscle diseases and chronic fatigue syndrome. The Committee recommends that research be carried out into the effectiveness of CBT in patients suffering from persistent complaints after a bout of Lyme disease or whose complaints are attributed to Lyme disease.

9.4 Gaining a greater understanding

In the course of the advisory process with regard to Lyme disease, the Committee unearthed several gaps in the scientific knowledge on this topic. In this connection, the Committee cites examples such as pathogenesis and co-infections with other micro-organisms. Various additional points emerged from the focus groups, for example. Research is needed to fill these gaps.

- The Committee recommends setting up a study into patients with confirmed cases of Lyme disease. By monitoring them over a period of time, it should be possible to determine whether there are predisposing (bacterial, immunological) factors for the development of late-stage Lyme disease and, if so, how this process might be influenced.
- The Committee also recommends that research be carried out into the relevance of co-infections with other micro-organisms transmitted by ticks and, if it proves necessary, to improve the diagnostic procedures for these micro-organisms.

9.5 Developing and compiling knowledge and expertise

In the Netherlands, physicians treating Lyme disease patients exhibit a degree of variation in their expertise and approach. Physicians in primary and secondary healthcare sometimes feel ill-equipped to treat (or meet the requirements of) Lyme disease patients (especially those with late-stage Lyme disease) or patients who attribute their complaints to Lyme disease. The more highly specialised treatment centres in secondary and tertiary healthcare each have their own individual approaches. There is also a shortage of specialised psychological experts. Accordingly, the Committee has formulated the following recommendations:

- There is a need for a unified, multidisciplinary approach (including psychological expertise) to the treatment of patients with late-stage Lyme disease, in particular, and of patients whose complaints are attributed to Lyme disease.

- The Minister of Health, Welfare and Sport's recommendation concerning coordination between specialised treatment centres for Lyme disease merits implementation. In addition, helping to set up a network, for example, might contribute to a more uniform approach.
- GPs with extensive experience in the field of Lyme disease could be invited to participate in this network. At the same time, the network could also serve as an information resource for physicians with less experience in this area.
- An integrated approach will enhance the impact of the existing shortage of psychological expertise. Accordingly, such expertise will need to be further developed and incorporated into the treatment centres.
- In addition to being a source of knowledge, a network of specialised treatment centres is a potential source of research data on Lyme disease patients and on the disease itself. The network must be structured to facilitate the collection of such data.
- It would be helpful if an inventory were to be made of those physicians who have received training (and continuing education) in the diagnosis and treatment of Lyme disease. If necessary, the number of training programmes and continuing education programmes should be increased.

Academic collaborative centres offer a format in which the roles of multidisciplinary patient care, training, research, knowledge sharing and implementation can be combined. A collaborative centre of this kind could acquire an international dimension by seeking to coordinate its research activities with those currently being launched in the UK, in line with the process initiated by the James Lind Alliance. The Committee has put forward this organisational form as a suggestion.

9.6 Improving the provision of information

From the perspectives of those affected there appears to be a great need for the provision of clear and reliable information. This information can be delivered via the Internet, as well as in the form of information materials available at nature centres, parks and hiking areas. Given the scale of the Lyme disease problem and the conflicting information that is currently available, the Committee feels that this issue should be dealt with by the government. The Committee feels that, in addition to the Ministry of Health, Welfare and Sport, other ministries should be involved. It welcomes the various initiatives that have already been undertaken, and would like to supplement them by making the following recommendation:

- Not only should the measures taken to enhance information provision be designed to facilitate assessments of their effectiveness, but such assessments must actually be carried out.

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Annexes

Annex

A

Request for advice

Letter dated 27 April, 2011, from the President of the Dutch House of Representatives to the President of the Health Council:

Dear Prof. Gunning-Schepers,

On 26 April, under Article 30 of the Standing Orders of the Dutch House of Representatives, the House decided to ask the Health Council’s advice about the Council regarding aspects of the Citizens' Initiative by the Dutch Association for Lyme Patients, which is being dealt with by the Standing Committee on Health, Welfare and Sport. Specifically, the issues in question concern the current level of knowledge in the fields of diagnosis and therapy, as well as useful lines of enquiry for future research projects into Lyme disease.

The Dutch House of Representatives would be very grateful if the Health Council could deliver its advice before the end of the year.

You will find details of the Citizens’ Initiative in the annex.

Yours faithfully,
(signed)
Gerdi A. Verbeet
President of the Dutch House of Representatives

Annex

B

The Committee

- Prof. S.W.J. Lamberts, *chairperson*
  Emeritus Professor of Internal Medicine, Erasmus MC, Rotterdam
- Prof. P.J. van den Broek
  Emeritus Professor of Infectious Diseases, Leiden University Medical Center, Leiden
- Dr. N.D. van Burgel
  medical microbiologist, HagaZiekenhuis (Haga Hospital), The Hague
- Prof. H. van der Horst
  Professor of General Practice and Elderly Care Medicine, VU University Medical Center, Amsterdam
- Dr. K.E. Hovius
  veterinary surgeon, ‘t Heike animal clinic, Veldhoven
- Prof. M.J.H. Huibers
  Professor of Empirically-driven Psychotherapy, VU University Amsterdam, Amsterdam
- B. van Kooten
  neurologist, Gelreziekenhuizen (Gelre Hospitals), Apeldoorn
- Prof. B.J. Kullberg
  Professor of Internal Medicine and Infectious Diseases, Radboud University Nijmegen Medical Centre, Nijmegen

- Prof. J.W.M. van der Meer
  Emeritus Professor of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen
- Dr. H. Sprong
  project leader, tick-transmitted diseases, Centre for Infectious Disease Control Netherlands, National Institute for Public Health and the Environment, Bilthoven.
- J. Leek, *deputy observer*
  Ministry of Health, Welfare and Sport, The Hague
- C. Schenk, *observer*
  Ministry of Health, Welfare and Sport, The Hague
- Dr. M.F.M. Langelaar, *scientific secretary* (till 01-04-2012)
  Health Council, The Hague
- C.A. Dondorp, *scientific secretary*
  Health Council, The Hague
- Dr. K. Groeneveld, *scientific secretary*
  Health Council, The Hague
- Dr. V.W.T. Ruiz van Haperen, *scientific secretary*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex C

Individuals consulted (patients with first-hand experience and physicians)

- G. Bruijn, rheumatologist, MC Zuiderzee (Zuiderzee Medical Centre)/ Emmeloord
- H. Hutink, patient support group, Dutch Association for Lyme Patients, Amersfoort
- S. Huyshe-Shires, chairman Lyme Disease Action, Penryn, United Kingdom
- Dr. H.C. Klein, psychiatrist, neuroscientist, University Medical Center Groningen
- M. Mud, member of the board of the Dutch Association for Lyme Patients, Amersfoort
- J.S. van Os, cardiologist, Tjongerschansziekenhuis, Heerenveen
- G. Pekel, member of the board of the Dutch Association for Lyme Patients, Amersfoort
- Dr. D. Uitdenbogerd, petitioner, Citizens' Initiative on Lyme disease

Experts from the European Centre for Disease Control and Prevention, Dept. Emerging and Vector-Borne Diseases, Stockholm.

Participants in focus group survey, Athena Institute.

Annex D

UK's top 10 research questions concerning Lyme disease

1 What is the best treatment for children and adults presenting with a) early Lyme disease without neurological involvement and not including erythema migrans and b) late Lyme disease of any manifestation? To include consideration of drug(s), dose, duration.

2 What key questions (clinical and epidemiological) should be considered to help make a diagnosis of Lyme disease in children and adults in the UK and would a weighting table be useful?

3 How effective are the current UK tests in detecting infections due to the genospecies and strains of *B burgdorferi* sl in the UK and which single test and what combination of tests performs best in diagnosing or ruling out active Lyme disease. Should stage of the disease and patient age be taken into account when interpreting these tests?

4 What are the outcomes of cases where long term treatment has been used?

5 What is the optimal course of action if symptoms relapse after a treatment course is finished?

6 What is the optimal course of action if symptoms persist after initial treatment: should antibiotic treatment be continued until all symptoms have resolved or should a different dose or different antibiotic be used and what is the course of action if treatment appears to fail completely?

7 Are continuing symptoms following conventional recommended treatment due to continued infection, or an immune response or other process?

8 How common is relapse and treatment failure and is it related to disease stage, gender, co-infections or any other factor?

9 Are there long-term consequences if treatment is delayed?

10 Can Lyme be transmitted via other means: person to person sexually, transplacentally or by breast feeding; through organ donation; through blood transfusion?

Annex E

Research priorities focus group survey

Focus group	Research topics
Patients with short-term Lyme disease	1 Better, faster diagnosis 2 Physicians’ knowledge of symptoms 3 Expand public awareness
Patients with long-term (or longer-term) Lyme disease (submitted by the Dutch Association for Lyme Patients)	1 More scientific knowledge (within the Netherlands and elsewhere) 2 Improved techniques for diagnosis 3 Research into combination antibiotics and other treatments (e.g. immune support, detoxification)
Patients with long-term (or longer-term) Lyme disease (submitted by members of the Committee)	1 Research into treatment (duration of treatment, combination with other treatments, combination antibiotics) 2 Improve physicians’ knowledge of this area 3 International knowledge centre
Parents of children with Lyme disease	1 Improved techniques for diagnosis 2 National centre of expertise/EU cooperation 3 Improving physicians’ knowledge of this area/professional development for physicians
GPs	1 Validated questionnaires for chronic Lyme disease 2 Alternatives to antibiotics 3 Mechanism of post-infectious clinical picture of Lyme disease
Professional practitioners at increased risk of Lyme disease	1 Effect of Lyme disease on productivity 2 Is Lyme disease an occupational disease? 3 Summary of preventive measures (international)
Those engaged in recreational activities who are at increased risk of Lyme disease	1 Better, clearer information 2 Improved knowledge among physicians of the initial symptoms of Lyme disease 3 Potential/effectiveness of impregnated clothing