Lyme Disease Action Plan

ZonMw

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A plan of action for new knowledge of Lyme disease in research, practice and policy

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ZonMw

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ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research (NWO).

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Preface

'In response to the final debate on the citizens' initiative on Lyme disease the Dutch Minister of Health, Welfare and Sport has undertaken to involve the patients' association in drafting the research agenda and the commissioning of research'

This passage from the commissioning letter from the Ministry of Health, Welfare and Sport to ZonMw in 2014 signalled the start of a process that culminated in the document before you: an inventory of research topics that can be used to draft a research agenda that will serve as a basis for the commissioning of research. I should like to consider both the content of this document and the stakeholders who have shed light from various angles on the issues surrounding Lyme disease.

In terms of its content, this document is in fact broader than stipulated in the Ministry's commission, encompassing both research topics and other activities. This additional content is related to the goal ZonMw set itself when fulfilling the Ministry's commission, which was to take the knowledge produced by research '*… to improve the prevention, diagnosis and treatment of Lyme disease, to prevent damage to health from Borrelia infection and to improve patients' quality of life'*.

During the interviews ZonMw conducted with stakeholders (Lyme disease sufferers, healthcare professionals, researchers and policymakers) it became clear that other kinds of action were needed to effect the desired improvements. This included action to enable the performance of research or use of new knowledge in practice and policy. In other words, this document combines research topics and actions concerning specific issues and potential solutions for Lyme disease.

As we have said, people with various perspectives from various disciplines – patients, researchers, healthcare professionals and policymakers – have been involved in compiling this document. Some of them were interviewed, all attended the invitational conference in November 2015, and most were at the meeting to finalise the action plan and research agenda in January 2016.
ZonMw selected the participants on the basis of their knowledge and experience (professional or otherwise) and asked them to take part in a private capacity. Though their knowledge and experience are related to the organisation where they work, the researchers and professional policymakers and practitioners did not represent their organisation in this process. All participants are listed in the appendix.

The group helped to draft a document that presents a good picture of what the different participants believe is needed in terms of research and other activities to achieve the desired improvement in practice and policy concerning Lyme disease.

Several participants have formally endorsed this action plan (see appendix). Others have not done so, for various reasons, though they do regard the document as a good basis for drafting more detailed research agendas and for other activities. All participants thus acknowledge the importance of the action plan and have undertaken to collaborate on its implementation.

I would therefore call upon anyone with an interest in this issue – including those who did not participate in the process – to get involved with the action plan in order to improve the situation as regards Lyme disease. We have a particular interest in the Lyme Disease Centre of Expertise that is currently being set up, which could potentially explore the topics in more detail using this action plan as a basis, and convert them into action for practitioners and/or researchers.

Dr. Sjaak J. de Gouw, chair of the ZonMw Infectious Disease Control committee and chair of the Lyme Disease Action Plan

Plan of action for new knowledge of Lyme disease in research, practice and policy

Summary

The action plan on Lyme disease sets out a list of the actions (research and other activities) identified and discussed by representatives of patients, researchers, professional practitioners and policymakers at a number of sessions held between late 2014 and early 2016. Chapter 1 explains how the list was compiled.

Implementation of the action plan should ultimately improve both the practice of and policy on diagnosing, treating and preventing Lyme disease. It will also help create a good knowledge and research infrastructure. The action plan covers four main subjects (basic knowledge, diagnosis, treatment, prevention), which are explored in more detail in chapter 2. The final chapter presents the research topics and other activities regarded as necessary to bring about the desired improvements. The participants have prioritised three topics of research for each of the main subjects.

ZonMw facilitated the process of compiling the action plan on behalf of the Ministry of Health, Welfare and Sport, and at the initiative of two patients' associations, the *Nederlandse Vereniging voor Lymepatiënten* (Dutch Association of Lyme Disease Patients) and *Stichting Tekenbeetziekten* (Tick-borne Diseases Foundation). ZonMw is not the owner of the action plan. It is up to the stakeholders to arrange for its implementation. This inventory is only a starting point. Anyone who is planning an activity is advised to involve patients and other relevant stakeholders and experts in defining the objectives, desired results and an appropriate approach.

ZonMw is subsidising the first of the research projects in 2016. The research agenda for this call for proposals, drafted at the meeting of 26 January 2016, represents a more detailed selection of the topics previously prioritised.

Contents

Chapter 1 Introduction: the goal and structure of the Lyme Disease Action Plan

Between late 2014 and early 2016 patients (and others with knowledge gained through experience), researchers, professional practitioners and policymakers got together to identify in a number of phases the issues associated with Lyme disease and potential solution approaches. They did so at the initiative of two patient associations: the *Nederlandse Vereniging voor Lymepatiënten* (Dutch Association of Lyme Disease Patients) and *Stichting Tekenbeetziekten* (Tick-borne Diseases Foundation). ZonMw facilitated this process on behalf of the Ministry of Health, Welfare and Sport. This action plan is the result of that process. **Appendix 1** lists the participants in the process.

Goal of the action plan
The activities related to Lyme disease set out in this document are designed to make available more knowledge of Lyme disease in order to improve prevention, diagnosis and treatment, prevent damage to health as a result of Borrelia infection, and improve patients' quality of life. Lyme disease patients and current questions concerning recognition, diagnosis and treatment of the disease are the main focus throughout. Ways of preventing Lyme disease are also considered.

How did the action plan come about?
The action plan follows on from the interviews with stakeholders (2014-2015), the discussion paper[1] setting out the issues associated with Lyme disease and solution approaches (October 2015) and the invitational conference (12 November 2015), at which participants translated the solutions into specific proposals for research and activities in policy and practice. On 26 January 2016 the participants agreed that this action plan presents a good picture of what is needed in terms of research and other types of activities to bring about the desired improvements in practice and policy regarding Lyme disease.
The final version of the action plan is based on the outcomes of the invitational conference, the responses of participants in the external review following the conference, and several minor amendments made on 26 January, which are highlighted in the text.

Subjects
The action plan sets out the research topics and other activities on the basis of four main subjects: basic knowledge, relevant to every issue (K), diagnosis (D), treatment (B) and prevention (P). Research topics and other activities designed to lead to products that help achieve the desired improvement are set out for each main subject. The participants have prioritised three research topics for each main theme. Other types of activity have not been prioritised.

The document sets out for each of the four main subjects what the participants regard as necessary for the improvement of the prevention, diagnosis and treatment of Lyme disease and for a good knowledge and research infrastructure in terms of:
1. What research needs to be conducted?
2. What are the priorities for research?
3. What actions other than research are needed?
4. What specific products should research and other actions produce, and how can they help improve practice and policy?

[1] The *Discussiestuk voor een onderzoeksagenda over Lymeziekte. Van discussie naar nieuwe kennis over Lymeziekte in praktijk en beleid* ('Discussion Paper for a Lyme Disease Research Agenda. From debate to new knowledge of Lyme disease in practice and policy'), ZonMw, October 2015. Available from ZonMw; please email bloemers@zonmw.nl

BY whom and FOR whom?

The action plan was compiled by the participants at the invitational conference on 12 November 2015, who determined what its content should be from their various perspectives as patients/experts on the basis of experience, professional practitioners, researchers and policymakers. None of the participants is formally the owner of the action plan, however. ZonMw facilitated the process of drafting the action plan, but is not the owner. The action plan is thus for any interested party who wishes to use it as a basis for activities. It would be advisable for anyone planning an activity to involve other relevant stakeholders and experts in defining the objectives, desired results and an appropriate strategy. Some attempt was made to identify 'actionees' for the various parts. The results are not presented here, however, as there was not enough opportunity during the process for proper commitments to be made.

What next?

In 2016 ZonMw is subsidising the implementation of the first of the research topics. A further selection from previously prioritised topics was made for this call at the meeting on 26 February. This demonstrates how the action plan can be used as a basis for a research agenda.

Researchers will be canvassed for their interest in submitting proposals. Patient involvement in the procedure of awarding grants will take the form of a patient panel.

The action plan can also be used to develop other initiatives. For parties interested in conducting research or other activities, this document represents an up-to-date agenda for improvements to the diagnosis, treatment and prevention of Lyme disease. Anyone setting up a project on this basis can count on the collaboration of stakeholders, from patients to researchers, and from treatment providers to policymakers.

The following considerations are important when it comes to ensuring sufficient support among stakeholders for the implementation of the action plan:

- Develop products in accordance with the features set out in table 1 (chapter 3).
- Develop products on the basis of the actions (organised by main subject) in table 2 (chapter 3): research or other activities.
- Involve stakeholders: patients, professionals, researchers and possibly policymakers and/or private parties. It is advisable, when planning a project, to agree important points concerning results and objectives with stakeholders.
- Ensure that the products are also usable in attempts to improve the prevention, diagnosis and/or treatment of Lyme disease, prevent damage to health resulting from Borrelia infections and enhance patients' quality of life.

In short, the action plan helps achieve the specific objectives in the discussion paper as it can be used as a basis for a research agenda (goal 2) and a list of actions for policymakers and practitioners (goal 3). Translating actions into specific products shows how knowledge can be applied (goal 5). Finally, the involvement of patients, researchers, professionals and policymakers provides a sustainable base for research and activities related to Lyme disease in both the short and the longer term (goal 4).

Chapter 2 Products of the Lyme Disease Action Plan

Implementation of the action plan should lead to improved prevention, diagnosis and treatment of Lyme disease and create a good knowledge and research infrastructure. To guarantee there is a focus on practical application, specific products have been identified for each main subject (basic knowledge, diagnosis, treatment, prevention) that are designed to achieve the desired situation for the patient and for healthcare practice. This chapter lists the products under the four main subjects, followed by three research topics prioritised by the stakeholders.

Basic knowledge – products

Product 1 = Reference framework and categorisation into patient subgroups
Product 2 = Register and biobank of Lyme disease patients
Product 3 = Knowledge of presence of Lyme disease among patients with non-Lyme diagnosis (for new tests, diagnosis, guideline/decision model)
Product 4 = Knowledge of pathogenesis (for diagnosis, treatment methods, treatment guideline/decision model)
Product 5 = Knowledge of Borrelia infection (tick-borne diseases, other co-infections and routes of infection) (for diagnosis, treatment methods, treatment guideline/decision model)
Product 6 = Solutions to social issues associated with Lyme disease (social and work policy, testing, training, public information)
Product 7 = Strategy for dissemination and application of new knowledge of Lyme disease in a medical setting (for organisation, information for healthcare practitioners)

Basic knowledge – top 3 research topics

No. 1
Research on role of co-infections in onset of Lyme disease
No. 2
Research into properties of Borrelia bacterium and its 'behaviour' in humans; bacterium survival mechanism; how it 'disguises' itself in the body
No. 3 (two topics in 3rd place)
1. Borrelia infection in people with neurodegenerative and neurological disease (such as dementia, ALS and MS); ME/CFS; psychological disorders.
2. Research into immune system response to Borrelia infection and individual risk factors.

Diagnosis – products
Product 1 = Decision model for diagnosis
Product 2 = Knowledge of existing tests (for decision model, diagnosis)
Product 3 = Knowledge of new tests (for decision model, diagnosis)
Product 4 = Format for reporting test results
Product 5 = Reference centre
Product 6 = Training for treatment providers, public information
Product 7 = Patient information

Diagnosis – top 3 research topics
No. 1 (topics relating to new tests have been grouped together)
Research on new tests:
- for Borrelia (and variants) and co-infections
- for diagnosing active infection
- for neurological symptoms (SPECT/PET scan)

No. 2
Research to validate various tests currently used for Lyme disease diagnosis in the Netherlands and elsewhere
No. 3
Research for and development of a decision model for diagnosing Lyme disease

Treatment – products
Product 1 = Decision model for treatment
Product 2 = Knowledge of treating acute Lyme disease (and prevention of late symptoms) (for decision model, treatment methods)
Product 3 = Knowledge of treatment for late symptoms of Lyme disease (for decision model, treatment methods)

Treatment – top 3 research topics
No. 1
Research into promising new, unusual, ‘out of the box’ treatments, with focus on difference between adults and children.
No. 2
Research for validation of a Dutch questionnaire for monitoring treatment
No. 3
Research into influence of co-infections on the action and effect of treatment methods.

Prevention – products

Product 1 = Measures to prevent against tick bites (e.g. protection, public information, substances to combat ticks in environment)
Product 2 = Measures to prevent Borrelia infection (e.g. training for doctors, public information, blood bank policy, vaccination)
Product 3 = Measures to prevent onset of persistent problems after primary infection (training for doctors, decision model/guideline for treatment)

Prevention – top 3 research topics

No. 1

Research into minimum interval between tick bite and infection.[2]

No. 2

Research into possible routes of infection/transmission of Borrelia other than via tick bites.

No. 3 (two topics in 3rd place)

1. Research for development of a Borrelia or tick bite vaccine.
2. Public information: research into ways of improving education on tick bites for general public.[3]

[2] Identified at the meeting on 26 January 2016 as an ACTIVITY for which no research is required as yet.
[3] See footnote 2.

Chapter 3 Details of actions: research and other activities

This chapter sets out further details of the products and activities required to improve the diagnosis, treatment and prevention of Lyme disease and for a good knowledge and research infrastructure. **Table 1** provides details of products grouped by main subject, listing their features and how they can help improve practice and policy. The codes in the **Theme** column refer to the **Discussion paper** of 12 November 2015. **Table 2** sets out the actions (research and other activities) needed to develop these products.

Table 1 Product features

Products associated with **Basic knowledge**	Theme	Product features
Product 1 = Reference framework and categorisation into patient subgroups	K1	1. The reference framework should be based as far as possible on objectively observable features and symptoms reported by the patient. 2. One or more sets of symptoms should be identified that are typical of: - the concepts of 'non-specific symptoms' of Lyme disease, and 'persistent' and 'chronic' Lyme disease; - what patients actually experience (multisystem and fluctuating over time); - syndromes related to Lyme disease. 3. Categorisation of patients into subgroups important/useful for research and treatment. - Categorisation should be dynamic and temporary, and should be adjusted in response to new scientific knowledge. - When a categorisation into patient subgroups is used, consideration should be given to groups that do not clearly fall into one category. - Perhaps define an extra category.
Product 2 = Register and biobank of Lyme disease patients	K2	1. Registration should be linked to storage of biological material in a biobank. 2. Registration in primary, secondary and tertiary care 3. Register should include data on diagnosis and treatment. 4. The scale and scope of the group of patients in the register and biobank should take account of representation of the variety of patients, cost (as compared with benefits – scientific yield!), practicability. 5. If possible, include patients who have been abroad for treatment (how were they diagnosed and treated, what were the results of tests and treatment?). 6. Explore what additional information might be stored in the register/biobank. For example: a. images (e.g. photos of erythema migrans) b. genetic and epigenetic information, ranging from erythema migrans to any late symptoms (this is already being done at Radboud UMC and AMC)

		7. The register/biobank should make the following links/exchange of data possible: a. other Lyme disease registers and biobanks (including in other countries) b. pathology results (e.g. brain scans) at PALGA 8. Management of the register and biobank could be given to a centre of expertise or RIVM. Patients should also be involved. 9. Specifications for the structure, guidelines and tools for the register and biobank should be available to all parties wishing to collect data. The data should be accessible on the basis of the FAIR data principles (findable, accessible, interoperable, reusable).
Product 3 = Knowledge of presence of Lyme disease among patients with non-Lyme diagnosis (for new tests, diagnosis, guideline/decision model)	K2	1. Knowledge of the presence of Borrelia infection among people with neurodegenerative and neurological diseases (such as dementia, ALS and MS); CFS/ME; psychological disorders. Thyroid disorders? 2. Role and cause of these manifestations of Borrelia infection.
Product 4 = Knowledge of pathogenesis (for diagnosis, treatment methods, treatment guideline/decision model)	K3	Knowledge of pathogenesis should include: 1. The 'behaviour' of Borrelia bacteria in humans: manifestations, survival mechanisms in the human body and differences between different strains of Borrelia. 2. Immune system response to Borrelia infection and individual risk factors. 3. The progress of the disease and risk factors influencing it. 4. Description of the progress of the disease using the reference framework (product 1). 5. Characterise using disease markers, marker for active infection, reference values.
Product 5 = Knowledge of Borrelia infection (tick-borne diseases, other co-infections and routes of infection) (for diagnosis, treatment methods, treatment guideline/decision model)	K4	Knowledge of infection should include: 1. Microorganisms that can be transferred to humans by ticks at the same time as Borrelia (co-infection). 2. Influence of other infections already present (from flu to Q fever). 3. Routes other than tick bites that can lead to Borrelia infection. *(see also product 2 – Knowledge of measures to prevent Borrelia infection)*
Product 6 = Solutions to social issues associated with Lyme disease (social and work policy, testing, training, public information)	K5	The solutions should include: 1. Knowledge of the social issues associated with Lyme disease (e.g. incapacity for work, financial problems). 2. A training programme for people who encounter Lyme disease sufferers in a professional capacity (occupational medicine experts, company doctors, benefits agency staff and employment experts, GPs and neurologists).

		3. Test(s) of capacity for work. It should be noted that tests have limitations. The starting point should be what Lyme disease sufferers themselves and those around them say about the disease, their limitations and what they are able to do. 4. Website with information for patients on social issues associated with Lyme disease.
Product 7 = Strategy for dissemination and application of new knowledge of Lyme disease in a medical setting (for organisation, information for healthcare practitioners)	K5	The strategy should include: 1. An organisation that gathers information and knowledge of Lyme disease from other countries for application in the Netherlands. 2. An organisation for the dissemination of new knowledge of Lyme disease, as well as its correct implementation and application. 3. Centres that act as 'satellites' of the centre of expertise, where medical specialists and GPs can go for information in their own region. 4. Website with information for patients on medical issues associated with Lyme disease.

Products associated with **Diagnosis**	Theme	Product features
Product 1 = Decision model for diagnosis at all stages of the disease	D1	1. The decision model should help GPs and specialists: a. determine what diagnostic methods to use by considering the patient's symptoms (clinical picture) and any previous test results and treatments b. distinguish between adults and children c. distinguish between primary, secondary and tertiary care 2. The decision model should be dynamic/flexible: a. It should absorb new scientific insights. b. It should absorb information from long-term monitoring of a patient's clinical picture. c. It should be developed and updated in consultation with professionals and patients. 3. The decision model should consider: a. the patient's symptoms and use them as a basis (clinical questionnaire, patient subgroups) (*see also product 1, Basic knowledge*). It is no longer only about laboratory results. The patient should be given the 'benefit of the doubt' - 'Time' factor: monitor the patient over time and adjust policy if necessary - Evidence of the time since the tick bite and what this implies for the decision to test (there is currently as 6-8 week limit); b. the possible presence of co-infections; c. the uncertainty inherent in the test (sensitivity, specificity); d. the possibility that people with other diagnoses (such as dementia, ME/CFS, fibromyalgia, rheumatism, ALS or MS) might have Lyme disease (*also in product 3, Basic knowledge*).

		4. The decision model should clearly show which cut-off points have been chosen in the recommendation as to whether to treat and what the implications are: a. The chance that a patient will incorrectly not receive treatment (false-negative debate). b. The chance that a patient who does not have Lyme disease will incorrectly receive treatment. c. The risks of incorrectly treating associated with different treatment options. d. The consequences for the individual in question and for society (health, social, financial).
Product 2 = Knowledge of existing tests (for decision model, diagnosis)	D2	Knowledge of existing tests should cover: 1. the quality of various tests (including cellular tests) used in Lyme disease diagnosis in the Netherlands (and elsewhere) – both knowledge of intrinsic quality of tests and test kits, and their implementation); 2. the value of existing tests and test procedures (and reasons why results differ – validity? differences of interpretation?); 3. the limitations of existing tests; 4. the extent to which existing tests are suitable for use on children. 5. Knowledge should be updated on the basis of the national register.
Product 3 = Knowledge of new tests (for decision model, diagnosis)	D3	Knowledge of new tests should cover: 1. biomarkers - for diagnosing active Lyme disease - for monitoring the progress of the disease - using material from the biobank - international collaboration needed; 2. tests for Borrelia, variants and co-infections; 3. neurological and neuropsychological tests; 4. background information on patient characteristics (symptoms, diagnoses, treatments and outcomes, changes over time) to include in development.
Product 4 = Format for reporting test results	D2	1. A nationally applicable format for presenting the test result for the applicant (treatment provider). 2. Information on: - which test has been performed and what the limits of reliability are; - where the test was performed (in connection with reproducibility); - information on the test result (details important for interpretation).
Product 5 = Reference centre	D2	To safeguard the quality of Lyme disease diagnosis: 1. reference values must be established for diagnosis; 2. information from the national register of Lyme disease must be used; 3. recommendations will be issued regarding the acceptance of commercial test kits for use in the Netherlands; 4. the implementation of current diagnosis protocols will be monitored with regular proficiency testing schemes.

Product 6 = Training for treatment providers, public information		1. Training for GPs, specialists and nurses to create more Lyme disease expertise. 2. The decision model containing up-to-date information on diagnosis as background information for the treatment provider should be used.
Product 7 = Patient information		1. A decision aid is needed for patients (preferably in the thuisarts.nl format developed by the Dutch GPs' association NHG, as this has good reach among patients). 2. The decision aid (including references to information sources) should contain information on test properties (such as sensitivity, specificity) that give an idea of the value and/or limitations of tests.

Products associated with **Treatment**	Theme	Product features
Product 1 = Decision model for treatment	B1	1. The decision model should be flexible and absorb new scientific insights. 2. The decision model should lead to personalised medicine and: a. take the patient's symptoms (clinical picture) as the starting point for treatment choices (*see also product 1, K1 and D1*); b. link the clinical picture to the serology and other biological parameters; c. take account of the progress of Lyme disease in its various manifestations d. include separate factors for children; e. take account of any other tick-borne diseases and co-infections present. 3. The decision model should make clear any overlap in the categorisation of patients into subgroups, as for example in the Health Council report on Lyme disease (*see Basic knowledge, product 1 (Reference frame)).* 4. The decision model should distinguish between treatment of <u>acute</u> Lyme disease (preventing late symptoms and persistent Lyme disease) and treatment of late symptoms and persistent Lyme disease. ***NB** The following points of discussion from the invitational conference of 12 November 2015 are important for the development of a decision model:* *- categorisation of patients into subgroups* *- question of whether or not to treat when there is doubt as to whether a patient has Lyme disease*
Product 2 = Knowledge of treating acute Lyme disease (and prevention of late symptoms) (for decision model, treatment methods)	B2	Knowledge should include: 1. acknowledgement that treatments (antibiotics) currently used for early symptoms are <u>generally</u> useful; 2. awareness of the possible exception that early treatment can lead to *seronegativity*, but is sometimes not enough for *eradication;* 3. treatment of Lyme disease in children; 4. treatment of residual damage resulting from Lyme disease;

		5. physical and psychological symptoms and the effect of treatment on them. This includes the difference between treating infection and treating a disrupted immune system; the debate over trial treatment if no infection can be identified; 6. treatment options in the event of co-infections; 7. antibiotic protocols to prevent late and persistent illness.
Product 3 = Knowledge of treatment for late symptoms of Lyme disease (for decision model, treatment methods)	B3	Knowledge should include: 1. acknowledgement that later in the disease process treatments different from those appropriate early in the disease are needed. (Participants mentioned several examples. These must be properly recorded before choices are made regarding actions for this product); 2. the additional value of supporting therapies like physiotherapy, rehabilitation, psychotherapy; 3. options for patients who have not benefited from any therapy (please note, however: uncertainty as to whether there is persistent infection, damage, auto-immune disease). (*for the concepts of 'persistent' and 'chronic' Lyme disease, see also the Reference framework (Basic knowledge, product 1)*

Products associated with **Prevention**	Theme	Product features
Product 1 = Measures to prevent tick bites (e.g. protection, public information, substances to combat ticks in environment)	P	Measures should focus, among other things, on: 1. Preventing the increase in tick bites - value of impregnated clothing, tick repellents etc. - measures to stop ticks spreading (in the natural environment) 2. Public education campaigns should target: - children - active communication about risk-period exposure - warnings against entering high-risk areas
Product 2 = Measures to prevent Borrelia infection (e.g. training for doctors, public information, blood bank policy, vaccination)	P	Measures should focus, among other things, on: 1. possible routes of infection/transmission of Borrelia other than tick bites (*see also K4*); 2. minimum time after a tick bite in which infection can occur ('24-hour limit'); *NB Take note of already published knowledge on possibility of infection when tick attached for less than 24 hours* 3. a vaccine against the Borrelia bacterium; 4. a vaccine against tick bites (that could also prevent other tick-borne diseases).
Product 3 = Measures to prevent onset of persistent problems after primary infection (training for doctors, decision model/guideline for treatment)	P	Measures should focus, among other things, on: 1. prophylactic antibiotics or other prophylactic substances; 2. prevention of any second Borrelia infection and reduction of the probability of chronic illness.

Table 2 Actions required to achieve products

Basic knowledge	Actions for product		Prioritisation
Product	**Research**	**Other activity**	**(from ICL 12-11- 2015)**
Product 1 = Reference framework and categorisation into patient subgroups		Use reference framework and categorisation into subgroups in: scientific research, register/biobank, decision models, guideline, reference centre	Not put to vote
	No research question was put forward for this product. The following suggestions were made in the external review: 1. Research into one or more sets of non-specific symptoms (multisystem, fluctuating over time) that can be regarded as typical of Lyme disease. 2. Retrospective research into the relatively specific Bannwarth syndrome (PET/SPECT brain scan): identify set of more specific symptoms that can be distinguished from among the more non-specific symptoms		
		1. Produce list of clinical symptoms typical of Lyme disease, in collaboration with patients. 2. Set out definitions and/or descriptions for diagnosis, treatment, prevention. 3. Examine extent to which a categorisation into subgroups will aid the decision model. - Ensure that no patients are overlooked when categorisation applied. - Consider extra or multiple categories in addition to those in the Health Council advisory report. - Decision model should make clear the overlap with patient subgroup categories currently in use, such as the	Not put to vote

		categories in the Health Council advisory report on Lyme disease. *(see also Treatment, product 1 – decision model)*	
Product 2 = Register of Lyme disease patients and biobank		Use register and biobank for: scientific research, policy	
	No research question was put forward for this product.	1. Organise talks with doctors, research and patients aimed at reaching consensus on: a. the scope and inclusion criteria for the register and biobank; b. the selection of items for the register and biobank; c. a way of recording clinical symptoms clearly and in a structured manner (access to validated questionnaire and list of tests); d. organisation of registration and biobank (all biological samples need not be kept at the same location); e. where to start: where efforts are already underway (incl. internationally), e.g. registration as part of PROSPECT study; f. a standard for recording data that stakeholders in the field can use; g. the governance structure (the Lyme disease centre of expertise is the obvious candidate to develop and manage the register and biobank); h. the funding structure. ZonMw's stipulation: the register and biobank must work in accordance with the FAIR principles and use existing expertise. See the NFU's Data-4-LifeSciences (http://www.data4lifesciences.nl)	Not put to vote

Product 3 = Knowledge of presence of Lyme disease among patients with non-Lyme diagnosis		Use knowledge of prevalence of Lyme disease for: new tests, diagnosis guideline/decision model	
	1a. Research into presence of Borrelia infection in people with neurodegenerative and neurological disease (such as dementia, ALS and MS); CFS/ME; psychological disorders. 1b. What is the situation regarding people with thyroid disorders? 2. What are the role and causes of these manifestations of Borrelia infection?		**No. 3** **(11 votes for poster no. 9)**
		2. Seek collaboration and financing opportunities from funds for the disease or disorder in question	Not put to vote
Product 4 = Knowledge of pathogenesis		Use knowledge of pathogenesis for: diagnosis, treatment methods, guideline/decision model	
	1. Properties of Borrelia bacterium and its 'behaviour' in the human body. a. What survival mechanisms does it have? How does it 'disguise' itself in the body? b. How do these mechanisms influence the transition from acute Lyme disease to long-lasting symptoms (see point 8)? Research: - in vitro, test animals, biofilms etc. - dogs would seem to be a good test animal model - obduction material from deceased Lyme disease patients - align with Prospect study		**No. 2** **(20 votes for poster no. 1)**
	2. What is the natural progress of untreated Lyme disease?		No. 7 (5 votes for poster no. 4)

	3. How does the immune system respond to a Borrelia infection? a. What are the individual risk factors? b. What is the impact of self-limiting infection (seropositive but no symptoms) on wider health? c. What are the determinants of the transition from acute Lyme disease to long-lasting symptoms? (see also point 8)		**No. 3** **(11 votes for poster no. 6)**
	4. What is the relationship between variations in Borrelia genospecies and patient-reported/clinical symptoms? a. Are there clinically relevant differences in sensitivity to antibiotics in different genospecies and strains of B. burgdorferi sl.?		No. 8 (4 votes for poster no. 10)
	5. Are there biofilms and different morphological forms (such as cystic forms, L-forms or granules) of B. burgdorferi *in vivo*, and what is their influence on treatment?		No. 9 (3 votes for poster no. 11)
	6. What is the cause of motor and/or sensory symptoms in Lyme disease patients?		Not put to vote
	7. What is the impact of low vitamin B12 levels?		Not put to vote.
	8. What determinants (epidemiological, microbiological, genetic, immunological, clinical and psychological) have a bearing on the transition from acute Lyme disease to long-lasting symptoms?		Not put to vote. Point incorporated into topics 1 and 3.
	9. Research is needed into markers and values: a. Reference values for researchers and healthcare practitioners (diagnosis and treatment). b. A marker of active infection.		Voted on in the category Diagnosis (product 3 – new tests)

	c. Disease markers for monitoring and describing the progress of the disease.		
Product 5 = Knowledge of Borrelia infection (tick-borne diseases and other routes of infection, co-infection)		Use knowledge of infection for: diagnosis, treatment methods, treatment guideline/decision model	
	1. What is the role of tick-borne co-infections in the onset of Lyme disease, the progress of the disease and the emergence of long-lasting symptoms? - What microorganisms can be transferred to humans by ticks at the same time as Borrelia?		**No. 1** **(25 votes for poster no. 3)**
	2. What microorganisms in a co-infection are potentially pathogenic? - Under what circumstances? - How do these pathogens influence each other? - What influence do other, simultaneous infections (from flu to Q fever) have on Borrelia infection? - And on the onset, progress and treatment of Lyme disease?		No. 8 (4 votes for poster no. 8)
	3. What are the determinants for transition from: - contact to infection - infection to disease?		No. 5 (7 votes for poster no. 2)
	4. What are the individual risk factors (why does one person become infected while another does not)?		No. 4 (8 votes for poster no. 10)
	5. What other routes can lead to Borrelia infection (other insects, transfer via blood, other bodily fluids or donated organs from Lyme		No. 6 (6 votes for poster no. 12)

	patients, maternal transmission during pregnancy)?		
		7. Record co-infections in national register. Monitor characteristics of disease in patients with co-infection.	Not put to vote
Product 6 = Solutions to social issues associated with Lyme disease		Use knowledge of social impact for: social/work policy, testing, training, public information)	
	1. What are social issues are associated with Lyme disease?		Not put to vote
	2. How do long-lasting symptoms resulting from Lyme disease lead to incapacity for work?		Not put to vote
	3. What is the financial impact of Lyme disease (on patients and society)? (RIVM already working on this)		Not put to vote
	4. How can Lyme disease patients' capacity for work be reliably tested (incl. neurologically)?		Not put to vote
		1. Organise training on social issues associated with Lyme disease for professionals (GPs, occupational medicine experts, company doctors, benefits agency staff and employment experts, and neurologists)	Not put to vote
Product 7 = Strategy for dissemination and application of new knowledge of Lyme disease in medical setting		Use strategy for: organisation, information	
	1. How can new knowledge of Lyme disease be disseminated, implemented and applied in the correct way?	Proposed: 1. Lyme disease working groups in which all disciplines are represented, which meet once or twice a year. 2. Involve industry.	Not put to vote
		3. Establish centres that act as 'satellites' of the centre of expertise, where GPs can go for information.	

		4. Set up a website with information for patients on medical matters associated with Lyme disease	Not put to vote
		5. Dutch research groups and RIVM should establish what information and knowledge of Lyme disease is available abroad, and whether it is suitable for application in the Netherlands	Not put to vote

Diagnosis	**Actions for product:**		**Prioritisation**
Product	**Research**	**Other activity**	**(from ICL 12-11-2015)**
Product 1 = Decision model for diagnosis		Develop a decision model in accordance with features in table 1. Use diagnosis decision model in: guideline development/review, primary, secondary and tertiary healthcare practice, training	
		1. Review CBO guideline	(2 votes for poster no. 6)
	2. The decision model will help GPs and specialists: Explore how a decision model can incorporate individual patients' symptom patterns in consideration of what diagnostic techniques to use		**No. 3** (2+6=8 votes for poster nos. 1 and 2; ***combined with questions below: product 2(2) and 6***
	3. Decision model to be dynamic/flexible: Monitor progress of disease with aid of patient register. Perform observational research. See also Q fever strategy.		(0 votes for poster no. 7)

Product 2 = Knowledge of existing tests (for decision model, tests)		Use knowledge of existing tests for: decision model, testing, training/refresher training	
	1. Research for validation of various tests used for diagnosis of Lyme disease in the Netherlands and abroad. a. PET and SPECT, cellular testing. b. What existing tests are suitable for use on children? c. What are the characteristics of the tests? d. How do the tests perform in different laboratories? (consider interlaboratory comparison study) e. What is the impact of interval between infection and test on outcome of test? f. Perform a systematic review prior to conducting this research.	Align existing tests in terms of result (assessment) (1.d)	**No. 2** **(12+13 votes for poster nos. 10 and 11)**
	2. Research for validation of diagnosis questionnaire.	Group with Decision model (*see also: Treatment, product 2 – acute Lyme disease, study 4* (questionnaire about physical and psychological symptoms))	**No. 3** (combined) (8 votes for poster no. 6)
	3. Improve quality of existing tests - To what extent can the number of false positives be reduced by combining various tests?		(8 votes for poster no. 12)
	4. Research for evidence in support of time since tick bite and what this implies for decision to test (there is currently a 6-8 week limit). (*see also study 1f above*)		Not put to vote
		5. Develop a procedure for updating knowledge of existing tests with information from register.	Not put to vote

Product 3 = Knowledge of new tests (for decision model, testing)		Use knowledge of new tests for: decision model, testing, training	
	1. Research on new tests. 2. Research on biomarkers for diagnosing active infection. a. Use material from biobank. b. EM-positive patients can be used as starting point. c. Kinetics		**No. 1** (7 votes for poster no. 4, 2 votes for no. 14)
	3. Fundamental research on new tests for co-infections		19 votes for no. 15,[4] 17 votes for no. 16
	4. Fundamental research for the development of neurological and psychological tests (*also in product 2 – social issues, K5*)		Not put to vote
Product 4 = Format for reporting test results			
		When giving test result, explain the uncertainty associated with microbiological test results (in scientific publications, guidelines, patient information)	(1 vote for poster no. 13)
Product 5 = Reference centre			
		International collaboration on testing. Reference centre needed.	(6 votes for poster no. 5; 2 votes for poster no. 17)
Product 6 = Training, public information			
		Develop Lyme disease training for GPs and specialists. Include information on:	**No. 3 (combined)**

[4] NB: poster no. 15 covered two very different research topics: 'validate PET and SPECT' and 'new test for active infection'. It was not therefore clear what people voted for. The item is marked as 'D3', which suggests that 'new tests' is the intended topic. This problem was resolved by grouping the studies. PET/SPECT was added to product 2 (1).

		a. what EM can look like b. how to interpret test results c. the fact that the patient's clinical picture must be considered in the diagnosis	(2 votes for poster no. 3)
Product 7 = Patient information		1. Develop a decision aid for patients 2. (preferably in the thuisarts.nl format developed by the Dutch GPs' association NHG, as this has good reach). 3. The decision aid (with references to information sources) should contain information on the value and limitations of tests (such as sensitivity, specificity, margin of error, cut-off points, false negatives and false positives; no test can give 100% certainty)	Not put to vote

Treatment	**Actions for product**		**Prioritisation**
Product	**Research**	**Other activity**	**(from ICL 12-11-2015)**
Product 1 = Decision model for treatment		Use treatment decision model for: guideline development/review, primary, secondary and tertiary healthcare practice	
		Develop a decision model in accordance with features and points for attention set out in table 1.	
		Arrange easy access (for primary healthcare) to knowledge and experience of centre of expertise	Not put to vote
		Establish extent to which patient categorisation into subgroups is useful for the decision model. (*see also Basic knowledge, product 1 – Reference framework*)	Not put to vote
Product 2 = Knowledge of treating acute Lyme disease (and preventing late symptoms)	*NB the distinction between product 2 (acute) and product 3 (late) is not always entirely clear*	Use knowledge for: decision model, treatment methods, training, guideline development/review	

	1. Research into new or additional forms of therapy: a. that intervene in different manifestations of the Borrelia bacterium in the body (e.g. biofilm breakers/cyst breakers). b. Involve latest knowledge about clinical use of biofilm breakers (incl. against bacteria other than Borrelia). 2. Research new/unusual/promising/out-of-the-box treatments 3. Note difference between adults and children. Consider this in research.		**No. 1** (11 (7+4) votes[5] for poster no. 1; 8 votes for poster no. 2; 18 votes for no. 7) (18 (14+4 votes) for poster no. 7)
	4. Research into effect of co-infections on action/effect of treatment methods.		**No. 3** **(15 votes for poster no. 5)**
	5. Research for validation of a Dutch questionnaire for the monitoring of treatment. a. Inventory existing questionnaires; identify which ones are suitable for use (partially or in their entirety) in the Netherlands. b. Conduct questionnaire study to objectivise physical and psychological symptoms (and the effects of treatment – including alternative/complementary treatments – on them). c. Monitor patients over time using the questionnaires. d. Combine the outcome of questionnaires with knowledge of biomarkers.	Suggestions for survey of existing questionnaires: - consider translating and validating American questionnaires for use in the Netherlands - http://symcollect.de/de/	**No. 2** **(17 votes for poster no. 3)**

[5] The poster was voted on both separately, on nos. 1 and 7, as well as on the topics in combination (a line connecting 1 and 7), on the assumption that these topics should be combined. This idea was later abandoned. The 8 votes on the line connecting the two have therefore been split equally between the two separate topics (4 votes each).

	(*see also Diagnosis, product 2 – Existing tests (2)*)		
		6. Survey treatment methods/schedules used globally, both regular and complementary/alternative, and their effects (a systematic review)	(11 votes for poster no. 4)
	7. Research into optimum duration of antibiotic treatment: a. Weigh up potential benefits against side-effects. b. Outcomes of PLEASE study as a guide. c. Produce a systematic review of the effects of different treatment durations. d. Include fundamental research in survey of long-lasting symptoms/persistence (e.g. animal tests, in vitro studies) e. Consider the quality of the conclusions of studies and verify whether lack of evidence of treatment effectiveness might be the result of insufficient research.		(9 votes for poster no. 8)
	8. Study/develop treatment options for seronegative patients.		Not put to vote
Product 3 = Knowledge of treatment for late symptoms of Lyme disease (for decision model, treatment methods)		Use knowledge for: decision model, treatment methods, training, guideline development/review	
	1. Research into additional value of supporting therapies like physiotherapy, rehabilitation, psychotherapy		Not put to vote
	2. Research into treatment options for patients who have not benefited from any therapy.	When using cognitive behavioural therapy and other non-antibiotic treatments: - use only when it is clear there is no persistent infection;	Not put to vote

		- remain aware of the possibility that there may be an infection, as there is currently no test that can show active infection.	
Linked to Basic knowledge, product 2 – register and biobank		Record information on treatments in register	(8 votes for poster no. 9)

Prevention	**Actions for product**		**Prioritisation**
Product	**Research**	**Other activity**	**(from ICL 12-11-2015)**
Product 1 = Measures to prevent tick bites		Research for product one will produce knowledge for: - public information campaigns - tick repellents - substances to combat ticks in environment	
	1a. Research into ways of preventing any further increase in tick bites: - effectiveness of impregnated clothing, tick repellents etc. - possible damage to health from these substances - individual differences in sensitivity to tick bites (impact of skin microbiome or pheromones on likelihood of being bitten). 1b. Research into ways of preventing spread of ticks (in the environment). - Role of conservation management. - Tick control using nematodes.		(12 votes for poster no. 3)
	2. Public information: research into ways of improving education campaigns about tick bites for the general public. Including research on: - the effectiveness of public education about the danger of tick bites and what to do when bitten;	At the meeting on 26-1-2016 this topic was redefined as an ACTIVITY, for which no research is required for the time being	**No. 3 (15 votes for poster no. 4)**

	- the question of whether online information is enough, or whether it should be on display at every wildlife area; - tailor-made campaigns for specific groups such as the illiterate and non-Dutch speakers; - campaigns for employers and their staff who often work out of doors in wildlife areas; - tailor-made campaigns for professionals (GPs, paediatricians, company doctors etc.).		
Product 2 = Measures to prevent Borrelia infection			
	1. Research into possible routes of infection/transmission of Borrelia other than via tick bites. - maternal - sexual - via other animals - blood (implications for blood banks) (*see also Basic knowledge, product 5 – knowledge of infection*)	Research for product 2 will provide knowledge for: - training doctors - public information campaigns - blood bank policy - vaccination	**No. 2** **(21 votes for poster no. 2)**
	2. Research into minimum interval between tick bite and infection. *NB Note already published knowledge on probability of infection when tick attached for less than 24 hours*	At the meeting on 26-1-2016 this topic was redefined as an ACTIVITY, for which no research is required for the time being	**No. 1** **(25 votes for poster no. 6)**
	3. Research into development of a vaccine against: a. Borrelia, taking account of different subtypes b. ticks, tick bites The following applies to both topics: - Establish what can realistically be set in motion via this research agenda in a major process like developing a vaccine.		**No. 3** **(15 votes for poster no. 1)**

	- Where possible work with commercial partners/international research consortia. - Fundamental research into points of application for a vaccine (draw evidence from observations such as why one person develops Lyme disease after a bite and another does not). - Once an effective vaccine against Borrelia is available: * study the cost-effectiveness and acceptance of vaccination using that vaccine * consider whether the entire population should be vaccinated, or only high-risk groups - Consider whether an earlier vaccine withdrawn from the market would be a suitable starting point for vaccine development		
Product 3 = Measures to prevent onset of persistent symptoms after primary infection (doctor training, guideline)	1. Research into effectiveness of prophylactic antibiotics or other prophylactic substances ***NB*** *Wait for results of RIVM study of antibiotic prophylactic before launching this research* 2. Does a second Borrelia infection entail a greater likelihood of chronic illness than a first infection? ***NB*** *In the event that an infection occurs, there is development of Treatment product 2 (=Knowledge of treatment of acute Lyme disease (and prevention of late symptoms)*	Research for product 3 will provide knowledge for: - doctor training - guideline	(14 votes for poster no. 5)

Appendix List of participants

Ondertekening deelnemers actieplan lyme januari 2016

Naam	Organisatie	Ondertekening
Vertegenwoordiger uit ervaringsdeskundige		
Mw. D.E. Uitdenbogerd	Stichting Tekenbeetziekten	
Mw. E.H. Olthuis	Nederlandse Vereniging van Lymepatiënten	
Dhr. G. van Dijk	Nederlandse vereniging voor Lymepatiënten	
Mw. G.M. Pekel	Nederlandse Vereniging van Lymepatiënten	
Dhr. J.H. Bongers	Nederlandse Vereniging van Lymepatiënten	
Dhr. K.H.A.M. van Kempen	Stichting Tekenbeetziekten	
Dhr. K.T. Niks	Nederlandse Vereniging van Lymepatiënten	
Mw. M. Mud	Nederlandse Vereniging van Lymepatienten	
Mw. P. Poppen	Nederlandse Vereniging van Lymepatiënten	
Dhr. R.N. Mast	Stichting Tekenbeetziekten	
Mw. V.L. Broek	Stichting Tekenbeetziekten	
Mw. W.J.M. Elias- van der Lande	Nederlandse Vereniging van Lymepatiënten	
Vertegenwoordiger uit praktijk		
Dhr. D. Meijer	Artsenpraktijk Meijer	
Dhr. H. van der Linde	Mediversum	
Dhr. H.C.P.M. van Weert	AMC	
Mw. H. ter Hofstede	Radboudumc Lyme expertisecentrum	
Dhr. K.E. Hovius	Amphipoda	

Mw. K.U. Deutsch	Praktijk voor Integrale geneeskunde	
Dhr. S.J.G. Kingma	Oosteinde Walborg Kliniek	
Vertegenwoordiger uit onderzoekers		
Mw. A. Garritsen	Innatoss Laboratoties	
Prof dr. B.J. Kullberg	Radboudumc	
Dhr. C.W. Ang	VUMC	
Dhr. D. Notermans	RIVM	
Dhr. H.C. Klein	UMCG	
Mw. J.E.W. Broerse	Vrije Universiteit Amsterdam	
Dhr. J.W.R. Hovius	AMC	
Dhr. C.C. van den Wijngaard	RIVM	
Dhr. L.A.B. Joosten	Radboudumc	
Mw. M. Herremans	Innatoss	
Mw. M.E.J.L. Hulscher	Radboudumc	
Dhr. T.M.M. Scheepers	Pro Health Medical	
Mw. W.M. den Oudendammer	VU Athena Instituut	
Vertegenwoordiger uit beleid		
Dhr. A.M. Vollaard	RIVM	
Mw. C. Schenk	RIVM	
Dhr. H. Kroneman	UWV	
Mw. S. Wiessenhaan	Ministerie VWS	

The Lyme Disease Action Plan lists actions (research and other activities) identified and discussed by representatives of patients, researchers, healthcare professionals and policymakers at a number of sessions held between late 2014 and early 2016.

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