Cost utility analysis

OF THE CONTROL OF LYME DISEASE IN THE NETHERLANDS

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Title: A cost-utility analysis of the control of Lyme disease in the Netherlands

Abstract: Lyme disease, also known as Lyme borreliosis is a bacterial infection spread through the bite of an infected tick. In the last few decades, it is the most commonly reported vector-borne disease in Western Europe. Despite this evolving public health crisis, there has been little-to-no discussion of the cost and effectiveness of any preventive measures. This paper reviews the scientific literature to select the way to prevent LB based on scientific evidence. The cost utility ratio (CUR) of each measure are compared and their advantages and disadvantages are discussed. The major contribution of this paper is a set of recommendations for policy makers to find the way minimizing the economic impact of LB as well as reducing the disease burden in public health.

Key words: Lyme disease, control, cost-utility analysis, the Netherlands

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Introduction:

Lyme disease (LD) is an increasingly recognized multisystem, vector-borne zoonosis (Bhate & Schwartz, 2011). This disease, also known as Lyme borreliosis (LB), caused by spirochetes of the *Borrelia burgdorferi* sensu lato genospecies complex, is the most commonly reported tick-borne infection in Western Europe and North America (Wormser *et al*., 2006).

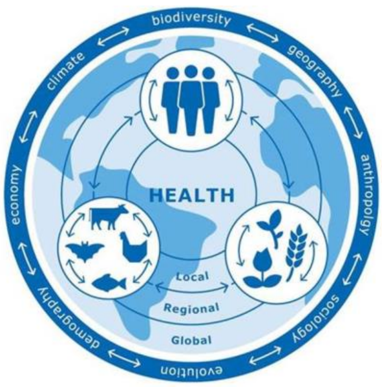
Stanek *et al.* (2011) pointed out that LB in Europe and in North America are very similar in their main clinical features, but differ in some aspects due to the greater variety of genospecies in Europe. In Europe the disease is generally referred to LB with the feature of erythema migrans (EM).

Due to the complexity of the ecology and epidemiology of LB, it's difficult to properly diagnosis as well as consequently monitor. Numerous efforts are put into preventive and control measures but mostly the effectivity are not being evaluated. At the same time, there is new economic study on LB in the Netherlands that it annually affect 32,500 patients and cost about 19.3 million euros. It is important to evaluate the effectivity of preventive measures for further.

This report is going to systematically review what interventions are used worldwide currently and investigate among them which one(s) is expected to be the most effective in the Netherlands. With the cost of each measure, find out which is expected to be the most cost-effective one(s) and furthermore, to estimate the utility of implementation of proposed measures in DALYs.

This research is part of a larger project called Emerging zoonoses in relation to the changing socio-economic environment (SocioEco2EmZoo). The project contributes to an improved insight into the main drivers of emerging zoonosis and will identify targets for intervention measures to reduce the economic and societal impact of emerging zoonosis and evaluate the policy implications of such interventions., which is the challenge accepted in both the strategic plan of WageningenUR (investment theme A Global One Health) and the NCOH strategic theme Emerging Infectious Diseases Preparedness.

The theme of Global One Health is about the health of people, animals, and their environments are closely connected: think of zoonosis, plant pests or other vector borne diseases. Understanding these interactions is crucial to safeguard the health of people everywhere on the planet. Besides these communicable diseases, a significant impact on public health is caused by global challenges, such as malnutrition, urbanisation and climate change. A Global One Health approach studies the effects created by this double burden and formulates strategies to control, mitigate and prevent them.



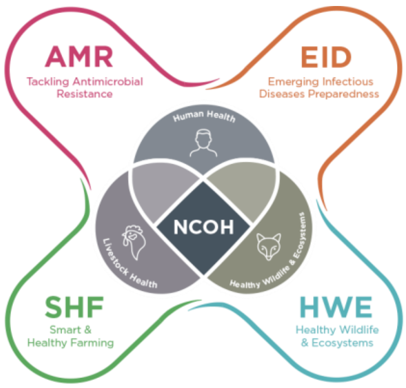


Figure 1. The theme of Global One Health Figure 2. Complimentary Research Themes

The 4 NCOH strategic research themes are complimentary and interactive. They focus on studying the interactions and connections between human, veterinary, wildlife, and environmental health in pursuit of durable solutions to grand societal challenges requiring a One Health approach.

Wageningen University & Research is partner of the Netherlands Centre for One Health. On March 9th 2017, Wageningen University & Research celebrated its 99th Dies Natalis. The theme of Dies Natalis 2017 is ‘Towards a global one health’.

During the Dies Natalis, part of this study is also presented in SocioEco2EmZoo project during a knowledge market.

In the next chapters, background information on LB will be provided, the methodological approach of the research will be described, results and future prospect will be discussed later on.

1. Background:

In this chapter, you will find the historic overview of Lyme Borreliosis(LB), the epidemiology and pathogenesis of LB, and the facts about its spreader, tick. Followed by the LB in a one-health context, finally the economics of LB the theories, methods and examples of evaluating the cost-effectiveness.

1.1 Overview of Lyme Borreliosis

The disease was first recognised as Lyme arthritis in 1976, named after the small town of Old Lyme, Connecticut, USA, where researchers from Yale University identified an unusual geographical cluster of suspected juvenile rheumatoid arthritis cases that were shown to be associated with tick bites (Steere *et al.*, 1977). Further studies led to isolation of an extracellular spirochaete from the deer tick, Ixodes scapularis, subsequently named *Borrelia burgdorferi* by Willy Burgdorfer (Burgdorfer *et al.*, 1982). Following recognising that infection by Borrelia can cause a multi-system disorder affecting a range of tissues including joints, skin, heart, nervous system, and some other organs but especially the whole spectrum (Steere *et al.*, 1977). The characteristic rash with central clearing known as erythema chronicum migrans appears in its first stage. But sometimes typical features may be absent, and important variations are evident among cases seen in different parts of the world (Bhate & Schwartz, 2011). Bacon *et al.* (2008) noted only about 50% of adults and 90% of children may develop into EM related with LB infection.

Epidemiology of Lyme Borreliosis

LB is difficult to diagnose clinically because of its complexity. Sensitivity of ELISA and immunoblot in the early phase of infection is low as it can take several weeks before an antibody response can be detected. Knowledge about its epidemiology and transmission may be of assistance when the diagnosis is unclear (Bhate & Schwartz, 2011). The nonspecific nature of many of its clinical manifestations presents a diagnostic challenge and concise case definitions are essential for its satisfactory management (Stanek *et al.*, 2011).

As a result, systematically reporting in LB data is limited and bias in both Europe and the US makes it difficult to reach reliable conclusions about LB epidemiology (Strle & Stanek, 2009). Few countries in Europe have made LB a compulsorily notifiable disease. Since the low awareness of Lyme and ticks, someone who was bitten by a tick or being infected with *B. burgdorferi* s.l. will not go to a general practitioner (GP) unless there is symptom emerging. Therefore, it is only possible to make approximate estimates of incidence of LB. A retrospective GP-study conducted by National Institute of Public Health and the Environment of the Netherlands (RIVM), via postal questionnaire asked nationwide GPs to provide the number of patients in their practice who had been seen in the previous year for tick bite or for EM rash illness (Hofhuis *et al.,* 2015). But in most countries assessment is mainly conducted through diagnostic laboratories reporting on the patients with positive tests (Stanek *et al.,* 2011). However, in daily practice, even GPs are often not well-educated about LB. It is hard for GP to recognise it is LB if the patient didn't mention was bitten by tick because the nonspecific symptom could lead to so many other diseases.

A report of a 1995 World Health Organization on LB diagnosis and surveillance provided estimates of the occurrence of LB in several European countries. Estimates of annual incidence ranged from 0.3 and 0.6 per 100,000 in the UK and Ireland, respectively, 16–39 in several central European countries, 55 in Bulgaria, and 120 and 130 per 100,000 in Slovenia and Austria, respectively. Annual numbers of cases ranged from 30 in Ireland to 20,000 in Germany, with a total estimate of 60,000 for the ten reporting countries (O'Connell et al., 1998).

In Europe, the disease occurs in localized areas of the British Isles and throughout continental Europe, with relatively high frequency in southern Scandinavia, The

Netherlands, parts of Germany and in eastern European states, such as Austria and Slovenia. Endemic levels are relatively low in France, Switzerland, Italy, Spain and Portugal, and the Balkan states. Tick bites and EM are positively associated with ecological factors like the proportion of the area covered by woods, sandy soil, dry uncultivated land, the number of tourist-nights per inhabitant and sheep population density.

Every year, LB is estimated to affect 85,500 patients worldwide, Europe 65,500, North America 16,500, Asia 3,500 and North Africa 10 approximately (Hubálek, 2009). From 1994 to 2009, a 3-fold increase was observed in GP consultations for LB in the Netherlands (van den Wijngaard *et al.*, 2015). This has led to public anxiety, incidents of unnecessary and potentially dangerous treatment (O'Connell, 1998) and restriction of recreational activities around forests, which may adversely affect the economies of LB affected areas.

Contrasting to the previously rising incidence of consultations for tick bites, a survey proceeded in 2014 by Hofhuis *et al.* showed the incidence decreased in 2014 to 488 consultations for tick bites per 100,000 inhabitants, i.e., 82,000 patients nationwide(Hofhuis *et al.*, 2016). This survey revealed a first sign of stabilisation of the previously rising trend in GP diagnosed EM, with 140 diagnoses per 100,000 inhabitants of the Netherlands. This equals about 23,500 annual diagnoses of Lyme-related EM nationwide in 2014, which results in a total amount of 1750 lost healthy life years every year (RIVM, 2016). Hofhuis also pointed out that in the 23,500 cases, about 1400 patients could be diagnosed with disseminated LB and 1000 patients with Lyme-related persisting symptoms (Hofhuis *et al.*, 2016).

Pathogenesis of Lyme Borreliosis

In the Netherlands, roughly 20% of adult ticks are infected with *B. burgdorferi* s.l. compared to 10% of nymphs and 0.62% of larvae (Rauter & Hartung, 2005, van

Duijvendijk *et al.*, 2016). Non- infection larval ticks acquire *B. burgdorferi* by taking a blood meal on infected animals, mostly small rodents, for example mouse. *B. burgdorferi* is then transmitted by nymphs and adult ticks to various other hosts, such as birds and rodents, large mammals and human beings (Ursinus, Coumou & Hovius, 2016). In Europe, a recent review identified nine small mammals like rat and mouse, seven medium-sized mammals (especially squirrels and hedgehog) and a number of birds as competent hosts of human pathogenic strains (Gern *et al.*, 1998). In the Netherlands, roe deer is the main and primary host for the adult tick stage. Therefore exclusive fencing is widely adopted in the roe deer habitats.

As ticks spend more than 90% of their time in the top soil and in the lower parts if the vegetation, the thickness of the litter layer is key determinant of survival rate and activity levels (van Wieren & Hofmeester, 2016). Hence, regularly mowing the vegetation and blowing the litter layer seems a good way to decrease the presence of ticks in certain area.

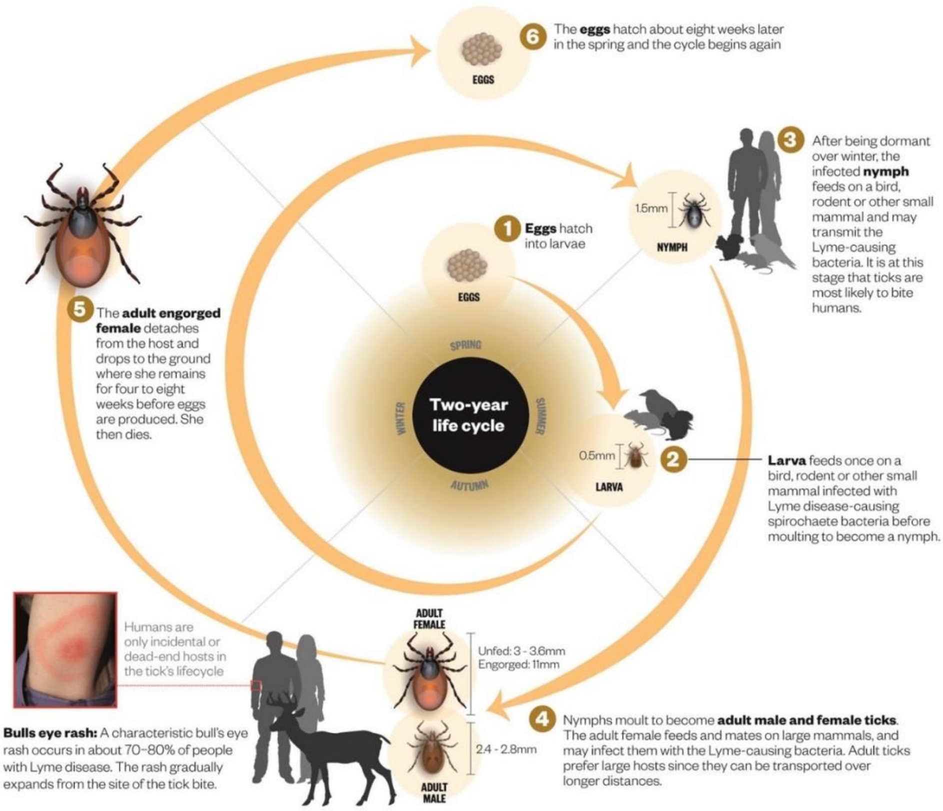


Figure 1. Life cycle of the tick (Delany, 2016)

Source: ECDC, CDC and University of Bristol.

Incidence of getting a tick bite

The distribution of LB in Europe is discrete. The risk of acquiring LB is intimately linked to tick abundance and exposure. High risk is not only associated with residency in rural areas, but also with occupation (e.g. forestry work) (O'Connell *et al.,* 1998; Gray, 1999) and with recreational and leisure activities (e.g. hiking, camping and berry picking) in high vegetation area. Furthermore, the relatively low abundance of ticks in some urban areas (e.g. private gardens and city parks) poses a substantial risk as well, because of the elevated exposure of visiting flowrate. Urban parks for the public may also pose a significant risk (Guy and Farquhar, 1991).

Based on a population survey, approximately 1.1 million tick bites were noticed in the Dutch population in 2007 (Hofhuis *et al.,* 2015). In another Dutch study, Mulder *et al.* (2013) determined the habitats and activities at risk for tick bites for people of different age categories using reports of Dutch citizens. Most people, 43%, were bitten in the forest, and an unexpected large number of people reported tick bites from their gardens (31%). Hiking, hobby gardening, and playing were the most-mentioned activities during which tick bites were received; people aged from 50 to 69 and children below 10 were bitten most. These clues pointed out that more than 70% of exposures are during the leisure time in green area. A third (34%) of the cases enrolled with EM did not recall preceding tick bites (Mulder *et al.,* 2013).

The basic risk definition is exposure times hazard. In every sixty tick bites in the general population, one consultation for EM at the GP was observed, resulting in an estimated risk of a *B. burgdorferi* s.l. infection approximately 2%, and for severe manifestations 0.2%. Thus most tick bites do not lead to the disease burden due to LB. In addition, the high incidence of localised LB only contributes limited impact to the disease burden in patients that can be successfully treated with antibiotics. In contrast, the relatively small incidences of both disseminated LB and persisting symptoms attributed to LB are causing a relatively high disease burden, and are considered to be a major public health concern. The high disease burden in these categories might already be reduced by improving the diagnosis and treatment of earlier stages of LB. Sprong & van den Wijngaard noted in the article *Prevention of Lyme borreliosis after a tick bite* that conventional measures to prevent tick bites, such as wearing protective clothing, using repellents, checking body and removing ticks, are simple ways to prevent at the beginning and stop the development of all stages of LB. In addition, advising people with a skin rash after a tick bite to visit a general practitioner can help to prevent the development of later stages of LB (Sprong & van den Wijngaard, 2016)

Novel measures, such as point of care testing and post-exposure prophylaxis have not yet been proven to contribute to the prevention of the disease. Although in 1991, Guy and Farquhar had already found that the high risk in urban parks, where people usually will not think about risk exists. Mulder *et al.* suggested that further investigations should also focus on urban areas, where the hazard and nature values might be low but where exposures is extremely high, such as parks and (private) gardens (Mulder *et al.*, 2013).

To reduce the exposure, recommended measures could be health education, campaigns and public health communication, focusing on behavioural measures, including avoidance of areas inhabited by ticks, performing routine body checks after exposure, using protective clothing and the application of tick repellents.

Another valuable management tool that would facilitate interaction and collaborate between nature management and public health is the generation of local risk maps, for example www.tekenradar.nl founded by Arnold van Vliet, who works as a biologist as well as communicating science to the public. He also suggested that using mass media could gain much more attention from the public.

The campaign was coordinated by the Dutch phenological network Natuurkalender (Nature's Calendar), which comprises organisations such as Wageningen University and the popular nature and wildlife radio programme Vroege Vogels (Early Birds) was launched every Sunday morning from 2001.

Other efforts like the Week van de Teek (week of the tick) (www.weekvandeteek.nl), supported by National Institute of Public Health and the Environment of the Netherlands (RIVM), and Wageningen University, together with other stakeholders, have prompted extensive national media attention on Lyme borreliosis each year around April, with a national awareness week on tick bites to mark the onset of the tick bite season. The RIVM distributed annually updated campaign materials for public health education of the general population on the prevention of tick bites and LB (communication toolkits on http://rivmtoolkit.nl/Onderwerpen/Teken_en_lyme), and published a national guideline for professionals on the prevention, diagnosis, and treatment of Lyme borreliosis (LCI, 2016).

A cost effectiveness/utility analysis of all the interventions mentioned above is still largely absent in this area. Because the disease has large socioeconomic consequences, as will be further elaborated upon in Chapter 3, there is an urgent need to further educate the public to stimulate preventive behaviour. Furthermore, in terms of behavior, it is also notable that the gap between accessing to the knowledge and uptaking personal protective measures.

Clinical manifestations of Lyme Borreliosis

LB manifestations can be divided into a localised, early disseminated and late disseminated disease stage. Definitions for each of these stages have been described extensively in the paper of LB: clinical case definitions for diagnosis and management in Europe (Stanek *et al.,* 2011).

EM is the sole manifestation of early-localised LB. Typically, a circular red rash occurs where is bitten, with central clearing that slowly expands. Its size is more than 5cm in diameter and occurs several days to weeks after a tick bite. When a EM does not occur, is not witnessed by the patient nor recognised by the physician and remains untreated, *B. burgdorferi* s.l. can disseminate through the lymphatic and blood system to other distant organs and tissues, such as the nervous system (NLB), the joints (Lyme arthritis) or the skin sites (acrodermatitis chronica atrophicans, ACA).

In Europe, most of the patients (77%-89%) are diagnosed with the first local stage of LB, with the feature of EM. In a minority of patients (10%-23%) are untreated in time and develop into disseminated LB and further persisting symptoms (Huppertz *et al.*, 1999). ACA (1-3% of LB patients in Europe) is a late and persistent phase with a slow and progressive skin condition which can develop even up to ten years.

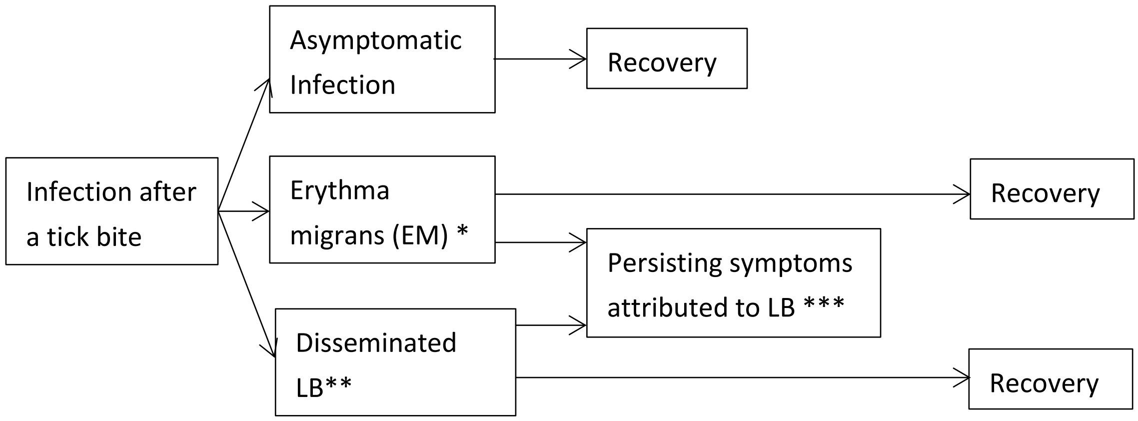


Figure 2. The outcome tree of a tick bite
Which cause the disease burden *0.005 DALYs per patient
**0.262 DALYs per patient **1.661 DALYs per patient

Preventions of LB

The risk of acquiring LB is intimately linked to tick abundance and exposure. An increased risk is not only associated with residency in rural areas, but also with occupation (e.g. forestry work) and with certain leisure activities (e.g. hiking, camping and berry picking) in high vegetation areas. More than 70% of exposure happens during the leisure time in green area (Mulder *et al.,* 2013). Furthermore, the relatively low abundance of ticks in some urban areas (e.g. private gardens and city parks) poses a substantial risk as well, because of the elevated exposure rate of visiting flowrate.

In theory, individual or community measures could apply very effective preventive methods. For example, in order to decrease the risk of tick bites and *Borrelia* transmission, people living in or visiting tick infested area are advised to avoid tick habitats, to wear long, light coloured trousers and to tuck them into their socks and to use insect repellent that contains permethrin or DEET on clothes or directly on skin. These behavioural measures are of great importance.

Mowbray, Amlôt & Rubin note that several interventions have been designed over the years and in different places to tackle the problem of people getting tick bites and contracting LD. However, it appears that the effectiveness of these interventions is often not known. In their article, Mowbray, Amlôt & Rubin (2012) reviewed previous studies that conducted such interventions that also assessed the effectiveness of the designed interventions. Of the 386 articles that were potentially relevant for their review, only nine included an assessment of the effectiveness of the intervention. One of the conclusions of the national expert consultation was that efforts concerning education on ticks and LB should be intensified and centrally coordinated by RIVM, as this is currently the most straightforward approach to prevent LB.

1.2 One Health approach

In recent years, the concept of "One Health" was adopted by many (inter)national organisations as a promising way to improve public health interventions. Controlling the risks of disease outbreaks and reducing endemic infectious diseases are crucial to food security, public health, climate change and biodiversity. It is a challenge, however to bring the One Health concept into practice.

'A Global One Health' reflects the interconnectedness and global nature of health care for humans, animals, plants and the environment. Many health risks can be controlled through effective interventions consisting of an adequate and varied food supply, hygiene, medicines, vaccines, vector control and crop protection. A sustainable and shared approach requires an integrated analysis of infectious diseases, with contributions from various knowledge domains including veterinary, public health and economic. Through a system approach, it provides an essential contribution to improving the health of people, animals and plants (WUR, 2016).

In the last decade, efforts to improve the collaboration between the public and veterinary health, has paid off (Wendt *et al.*, 2015). Since the transmission cycles of the pathogens causing LB occur mostly in nature, related with both ecology and economics, involvement of stakeholders of forest and nature management is a logical next level (Braks *et al.*, 2011). A Dutch research programme called "Shooting the messenger" involved the green domains and focused on the development of a One Health approach for the prevention of LB and other tick-borne diseases.

Epidemiological measurements to assess infectious diseases are reducing disease incidence, disease burden (van den Wijngaard *et al.*, 2015) and cost of illness. Cost of illness is most commonly measured in monetary terms and is used in combination with disease burden to prioritize health care issues. Knowledge on the costs of illness is also required for the calculation of cost effectiveness of potential intervention strategies such as vaccination campaigns (Šmit & Postma, 2016).

1.3 Economics of Lyme borreliosis

Although it has been argued that due to the complex ecology of LB it is difficult to implement preventive measures (O'Connell, 1998), the decreased incidence for tick bites consultations means that current interventions to prevent LB are effective. Examples of preventive measures are, for instance, reducing tick exposure in the forest, education on how to remove the tick quickly and correctly after being bitten and proper treatment etc. are easily accessible online(RIVM, 2017). Remarkably, the number of studies aiming at the effectiveness is not clear. These measures at different stages of the epidemiology of LB are thus difficult to compare. However, each of these measures does need resources and for decision makers such as the government it is useful to have insight in the cost-effectiveness of disease management. So in this report, lots of assumptions and estimation are used to carry out an advice for the decision maker.

Disease burden

With disease burden, the quantity of health loss in a population, caused by a disease, is meant (Murray & Lopez, 1997). The parameter used to measure the burden of disease, is the DALY (Disability Adjusted Life-year). This concept originates in the Global Burden of Disease (GBD) study by the World Bank and the WHO.

With a DALY, researchers try to express the loss of health in a number, taking into account two components (World Health Organization, 2010):

- The number of Years of Life Lost (YLL).

- The number of Years of Life with Disability (YLD).

When calculating the number of years lost by disease (YLL), the number of deaths by disease (N), as well as the life expectation at the age of the death (L) is taken into account:

YLL = N x L

When calculating the number of years lived with a disease (YLD), the average duration of the illness until diminishing or disappearing of the symptoms (remission) or death, are taken into account. This number is calculated by multiplying the number of cases (I), with the weighing factor for the severity of the disease: the Disability Weight (DW). In this weighing factor, zero equals a perfect health, and one equals death. Disability Weight scores can be found in the WHO database (World Health Organization, 2004). These components together, lead to the formula for the number of years lived with a disease:

YLD = I x DW x L

A DALY is calculated by adding the YLL and the YLD components. The formula for DALY is as follows:

DALY = YLL + YLD

I know it is a bit confusing, but DALY's as burden of a disease is the definition of WHO.

Cost-of-illness

In literature, the term "cost-of-illness" (Rice, 1969) or "COI" is referred to public costs. COI is also a burden of disease, but in monetary terms considered from a government's or society's perspective. Most authors differentiate direct and indirect costs. Direct costs are costs that are directly related to an illness, including expenses for prevention, protection, treatment, rehabilitation, education and research and investments in medical services (Rice, 1969).

Some authors further divide the direct costs into medical and non-medical costs. Medical costs can further be divided in ambulant, residential and pharmaceutical costs. Non-medical costs contain the costs resulting from the transportation of patients and social services (Luppa *et al.*, 2007).

Indirect costs can be divided into morbidity costs (i.e. the public costs resulting from the absenteeism or the loss of labour productivity caused by illness), and mortality costs (i.e. the public costs due to death). Sometimes, next to direct and indirect costs, a third category is added, being the "intangible costs". These are the costs coming from the loss of quality of life, both for the patient and his family (Luppa *et al.,* 2007). One can argue that the intangible costs can be represented by DALY or QALY.

1.4 Cost-effectiveness analysis and cost utility analysis

The effectiveness of preventive measures can be studied with cost-effectiveness analysis (CEA) or cost utility analysis (CUA). In cost-effectiveness analysis, the ratio of net health-care costs to net health benefits provides an index by which priorities may be set.

The net costs of an intervention are the total costs spent on that intervention minus any benefits gained by implementing the measure. It is necessary to calculate the net costs of independent interventions so that they can be compared to each other. Independent means that the costs and effects of one intervention are not affected by the introduction of another intervention

CEA compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money. Developed in the military, CEA was first applied to healthcare in the mid-1960s and was introduced to clinicians by Weinstein and Stason in 1977. "If these approaches were to become widely understood and accepted by the key decision makers in the health-care sector, including the physician, important health benefits or cost savings might be realized."(Warner & Hutton, 1980). This informs decision-makers who have to determine where to allocate limited healthcare resources to improve the public health.

CUA is the most common and well-known application in pharmaco-economics and is a way to compare preventive measures that can be used in the control of LB in the Netherlands. Such an analysis has not been provided for LB in the Netherlands, nor for other countries. CUA is a formal economic technique for assessing the efficiency of healthcare interventions. It is considered by some to be a specific type of cost-effectiveness analysis in which the measure of effectiveness is a utility- or preference-adjusted outcome (Coons & Kaplan, 1996).

The use of DALY's or QALY's is based on the expected utility theory, which is an approximation of behaviour under uncertainty. It has a number of rival theories, such as standard gamble and time trade-off, which are held to provide better descriptions of actual behaviour. However, for those other theories, individuals must be able to judge utility across different health states (Drummond *et al*., 1997).

DALYs and QALYs are technically similar in that they both express health in time (life years) and give a weight to years lived with a disease, both measures are HALYs (Health adjusted life Years). Gold *et al.* give a comprehensive review of the differences between DALYs and QALYs. DALYs measure health loss and QALYs health gain so they express an inverse value, as is illustrated by the weight for death (1 for DALY, 0 for QALY). More importantly the measures originate from different disciplines, which causes the disease weights to be measured in a different way with a different interpretation, resulting in different values. There is debate about the use of QALYs vs DALYs (Sassi, 2006) as they give different outcomes, but a large part of the differences is explained by whether or not age weighting and discounting is applied in the original DALY formulation(Murray, 1994).

When using a cost–utility analysis in the evaluation of health care decisions, the outcome measure can be expressed as a QALY or DALY, comparisons can be made across therapeutic areas – using the QALY/DALY as the 'common currency'. Therefore, the cost per QALY gained or DALY saved can be compared with those of other interventions, or with a notional threshold value of what is considered to represent cost-effectiveness (Phillips & Thompson, 2003). That's why CUA is preferred above CEA in an economic evaluation in health related field.

Applying cost-utility analysis with independent intervention requires that cost-utility ratios (CURs) are calculated for each programme and can be placed in rank order:

$$\text{CUR} = \frac{\text{cost of intervention}}{\text{health effect (eg. life-years gained)}} \quad (\text{€ /QALY}) \text{ or}$$

$$\text{CUR} = \frac{\text{cost of intervention}}{\text{health effect (eg. life-years saved)}} \quad (\text{€/}\Delta\text{DALY})$$

The smaller the CUR, the lower net costs of an intervention to gain the same QALY or save the same DALY. If the CUR is below zero, the intervention does not produce any positive health effects

Guidelines for cost-effectiveness of interventions

In health economics studies, health improvements or losses are often expressed in quality adjusted life years (QALY) (Drummond *et al.*, 1997). Guidelines for cost-effectiveness of regular health care interventions in Dutch hospitals use up to €50,000 per QALY saved as the maximum cut-off value. For nation-wide prevention programme (e.g. anti-smoking campaigns), the threshold is €20,000 per QALY as the lowest reference value. Saving one QALY represents a bigger health improvement than saving one life year (Benedictus, Hogeveen & Berends, 2009).

Variability and uncertainty

As mentioned above, given that real-life data are often limited and/or absent, every model builder has to deal with some degree of uncertainty and methodological controversy (Drummond *et al.*, 1997).

Variability is defined as ''the inherent heterogeneity of a system''; e.g. variations in the length of the hospital stay of different patients. Uncertainty is usually defined as ''a lack of perfect knowledge about a factor in the model that represents the system'' (Vose, 2000). Variability cannot be reduced. However, with the availability of more information on a system, the uncertainty might be reduced. For example the incidence of illness is not known but is estimated from observational data on a sample of the population. The uncertainty in the incidence rate can be represented by a statistical distribution, e.g. a normal distribution is often used.

CEA and CUA are far from being a precise science, and there is often considerable uncertainty associated with the findings and wide variation around the estimate generated. Estimates of the cost-effectiveness varied enormously due to differing assumptions relating to the type of intervention, the duration of treatment, the number, severity and impact on quality of life (QoL) of relapses that occurred, and to which extent was compromised by the interventions (Phillips & Thompson, 2003).

Some examples

The vaccine against LB is not available on the market in Europe nowadays, but a cost-effectiveness analysis of the vaccine against LD conducted in the United

States shows that the vaccine is cost-effective only for individuals who live in areas where LB is endemic and who are frequently exposed to ticks(Hsia et al., 2002).

To assess the economic impact of LB, cost data were collected in 5 counties of the Maryland Eastern Shore from 1997 to 2000. Patients were divided into 5 diagnosis groups, clinically defined early-stage LB, clinically defined late-stage LB, suspected LB, tick bite, and other related complaints(which is different from the classification within this report). From 1997 to 2000, the mean per patient direct medical cost of early-stage LB decreased from $1,609 to $464 ($p<0.05$), and the mean per patient direct medical cost of late-stage LD decreased from $4,240 to $1,380 ($p<0.05$). The expected median of all costs (direct medical cost, indirect medical cost, nonmedical cost, and productivity loss), aggregated across all diagnosis groups of patients, was ≈$281 per patient. These findings will help assess the economics of current and future prevention and control efforts (Zhang *et al.*, 2006).

At the average national incidence of LB (0.0067%) in the US, the incremental cost-effectiveness of vaccination was $1,600,000 per case averted when a yearly booster was given for 10 years after the standard initial vaccination regimen of 3 inoculations at 0, 1, and 12 months. For populations with an annual LB incidence of 1% (the incidence in several well-defined geographical areas of the US), the incremental cost-effectiveness was $9,900 per case averted. Disease incidence had to exceed 10% before vaccination with yearly boosters became both more effective and more cost saving than no vaccination(Hsia et al., 2002).

In this case, CEA of vaccination is a helpful tool in the decision making process to include novel vaccines in a vaccination program or to extend current programmes. It was also expected that cost-effectiveness studies with the novel vaccines against LB will be performed in the near future.

A cost-utility study done by Renata Šmit and Maarten J Postma on TBE vaccines have been performed in Slovenia, Sweden, Finland and Estonia so far. In this study, data will be mainly analysed by a quantitative method, QALY. The result is illustrated as an incremental cost-effectiveness ratio from the two current Slovenian vaccination programmes compared to no vaccination respectively €15,128 and €20,099 per QALY gained from the view of the health care payer. From the view of the society vaccination is cost saving, mainly due to avoiding the high indirect costs and disease burden (Šmit & Postma, 2016).

2. Material and Methods

This research consists of three elements: a literature review, interview and questionnaire. A simulation model and performed analyses is developed by using Microsoft Excel. More detailed descriptions of them will be provided in the following paragraphs.

2.1 Literature review

Literature searches were conducted using the following electronic search databases: PubMed, Web of Science and Scopus. The following MeSh terms were used: "Lyme disease", "Lyme borreliosis", "prevention", "control", "management" , intervention", "Netherlands" "DALY", "DALYs per patient", "cost of illness", "disease burden", "economic impact", "cost-effectiveness" and "cost-utility". Chain referral sampling was frequently used hereby.

These terms were then used in combination with the disease in question, by using the Boolean operators AND and OR. The search combination below was used:

- (Lyme) OR (Lyme borreliosis) AND (prevention) OR (control) OR (management) OR (intervention)

- (Lyme)OR (Lyme borreliosis) AND (disease burden) OR (burden of disease) OR (burden of illness) OR (DALYs)

- (Lyme)OR (Lyme borreliosis) AND (cost of illness) OR (economic impact)

- (disease) AND(cost-effectiveness) OR (cost-utility)

An elaborate search gave 627 abstracts, which were screened one by one. After applying the inclusion and exclusion criteria, only 33 articles and 7 websites were deemed fit for the study into the costs of illness. In the appendix, a schematic review of all selected cost-of-illness studies is shown.

2.2 Interview and questionnaire

During the period from October 2016 to June 2017, numbers of in-person and email interview and questionnaire were carried out with the help of Cathelijne Kaat and Talitha Overeem, who translated a lot of materials from Dutch to English for me.

I selected the experts from different fields ranging from veterinary and public health to social scientists and eco-biologist, as well as different stakeholders (full list of expertise can be found in Appendix I). The semi-structured questionnaire (Appendix I) is built up by the information collected from literature and Internet which is elaborated in the background and discussion.

2.3 Model description

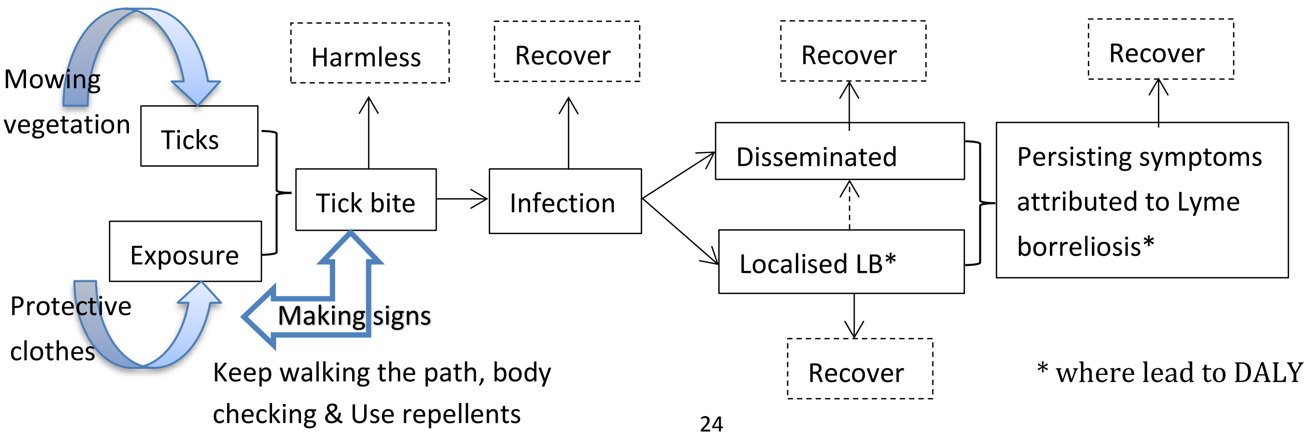
Study population and basic parameters

We followed a hypothetical cohort of 16.6 million population in the Netherlands, with a sex ratio 0.98 male/female, age range 0 to 100 years, and average remaining life expectancy 80 years. The model includes children and adults who get tick bites during their leisure time. Higher risk groups like professionals working in the green area were defined as proper protection were taken by themselves. We assumed that 10 000 000 individuals were infected annually on the basis of. We varied this number from 8 000 000 to 12 000 000 in sensitivity analysis(±20%).

Based on a population survey approximately 1.1 million tick bites were noticed in the Dutch population in 2007 (Hofhuis et al., 2015). According to data showing the infection ratio after a tick bite, we assumed that 5% of the population entered the model of the possibility of infected after tick bites.

For every sixty tick bites in the general population, one consultation for EM at the general practitioner was observed, resulting in a risk of approximately 2% for acquiring an EM after a tick bite. On the basis of available evidence (Sprong & van den Wijngaard. 2016), we assumed that 2% of infected individuals developed symptoms. In the basic case scenario, the R_0 (number of LB cases caused by each tick bite in a susceptible population) is approximately 23500 (Hofhuis et al., 2016). A time frame of one year was used because most costs and consequences related to LB occur during a single tick season, mostly during spring and summer. However, two key outcomes with longer-term effects, disseminated LB and persisting symptoms attributed to LB were included. Potential preventive measures are assumed to influence one or more of the following parameters. P_{visit} (the possibility of visiting woods), P_{TB} (the possibility of getting a tick bites), P_{inf} (the possibility of infected after a tick bites) and P_{LB} (the possibility of developed into a LB and lead to DALY) are parameters in the formulas which can be influenced by the preventive measures. As a basic (default) situation, the current situation in the Netherlands was used and the DALY's associated with that situation were estimated. DALYs due to LB after implementation of one of the selected measures were calculated with previous data. The difference in DALYs with or without a preventive measure was used in the estimation of the cost-utility. Following graphs show that how the exterminators effect the health outcome of LB

Figure 4. Outcome tree with possible health outcomes of LB.



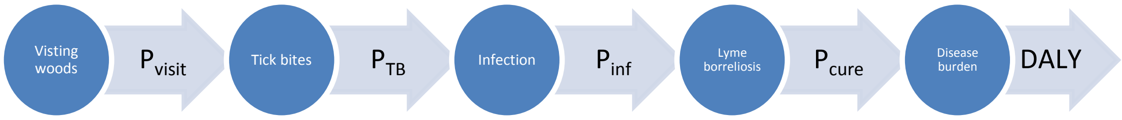


Figure 4. the exterminators and outcome of LB

The logical links between these exterminators are:

$N_{visit}=N_0*P_{visit}$

$N_{TB}=N_{visit}*P_{TB}$

$N_{inf}=N_{TB}*P_{inf}$

$N_{LB}=N_{inf}*(1-P_{cure})$

Where

N_0 is the number of population

N_{visit} is the number of visiting woods

N_{TB} is the number of getting tick bites

N_{inf} is the number of getting infection

N_{LB} is the number of LB cases

P_{visit} is the possibility of visiting woods

P_{TB} is the possibility of getting a tick bites

P_{inf} is the possibility of infected after a tick bites

P_{cure} is the possibility of a spontaneous recovery

Modelling

The cost calculation model contained the following equations:

1. Public health education and campaign materials for body checking and prompt tick removal and when to visit a GP
   $C_{edu}=C_m+C_h$
   $C_m=Q_l*C_l+ Q_p*C_p+ Q_b*C_b$...
   $C_h=Q_w*C_w$
   Where
   C_m=cost of materials
   C_h=cost of human resource

Q_l=amount of leaflets
C_l=cost of leaflet
Q_b=amount of brochures
C_b=cost of brochure
Q_p=amount of posters
C_p=cost of poster
Q_w=amount of working hours
C_w=salary per working hour

2. Making signs at the entrance and exit of the forest to remind
   1) Keep walking in the path (at the entrance)
   2) Body checking afterwards (at the exit)

   Arnold's advice

   $$\mathbf{C_s=C_d+(Q_{en}+Q_{ex})*(C_{s'}+C_{pl})}$$

   Where
   C_s=cost of signs
   C_d=cost of design a single sign
   C_{pl}=cost of place a single sign
   Q_{en}=amount of entrances
   Q_{ex}=amount of exits
   $C_{s'}$=cost of a manufacture a single sign

3. Wearing protective clothing

   $$\mathbf{C_c= Q_c*C_{c'}}$$

   Where
   C_c=cost of wearing protective clothing
   Q_c=amount of protective clothing
   $C_{s'}$=cost of a single protective clothing

4. Using tick repellents spray on body

   $$\mathbf{C_r=C_{r'}*Q_r*F_r}$$

   Where
   C_r=cost of repellents
   $C_{r'}$ =cost of a single repellent
   Q_r=amount of repellent
   F_r=frequency of using repellents

5. Regularly grass mowing and leaves removing

$C_m = Q_m * C_{m'} * F_m$

Where

C_m=cost of mowing(€/year)

Q_m=amount of mowing path(m)

$C_{m'}$=cost of a single moving on path(€/100m)

F_m=mowing frequency on path (year^{-1})

2.4 Parameterization

A deterministic static calculation model was developed in Microsoft Excel to estimate the costs and health outcomes for LB interventions. A schematic of the calculation model is shown in Table 1.

Table 1. Abbreviation and input value for the cost in LB calculation model

Parameter	Abbreviation	Distribution and value	Source
Cost of campaign[1]	C_{cam}	2 million	Assumed
cost of materials (€)	C_m	20 000	Assumed
cost of human resource (€)	C_h	50 000	Assumed
amount of leaflets	Q_l	10 000-100 000	Assumed
cost of leaflet (€)	C_l	300 over 10,000 flyers	https://www.drukland.nl/drukken/flyers
amount of brochures	Q_b	5000-10 000	Assumed
cost of brochure (€)	C_b	1000 over 10,000 brochure	https://www.drukland.nl/drukken/grote-oplage-geniete-brochures
amount of posters	Q_p	1000	Assumed
cost of poster (€)	C_p	15, A2 size	https://www.drukland.nl/drukken/fotoposters
amount of working hours	Q_w	5000	Assumed
salary per working hour (€/hour)	C_w	10	www.government .nl minimum wage
cost of signs (€)	C_s	16 000	Assumed
cost of design a single sign (€)	C_d	500	Assumed
cost of place a single sign (€)	C_{pl}	10	Assumed
amount of entrances	Q_{en}	3 per park	De Hoge Veluwe National Park
amount of exits	Q_{ex}	3 per park	De Hoge Veluwe National Park
cost of a manufacture a single sign (€)	$C_{s'}$	1.600 per 100 sign	http://www.homeadvisor.com/cost/safety-and-security/make-and-install-signs/
cost of wearing protective clothing (€)	C_c	80 million	Assumed
amount of protective clothing	Q_c	1 million	Assumed
cost of a single protective clothing (€)	$C_{c'}$	80, last for 6 months	Arnold van Vliet, personal communication
Using tick repellents	C_r	7 million	Arnold van Vliet, personal communication
cost of a single repellent	$C_{r'}$	10 per 100ml spray	AH.nl
amount of repellent	Q_r	7,313,000	Blije et al.,2010.

cost of mowing(€/100m)	C_m	6000	Verheyen & Ruyts. 2016
amount of mowing path	Q_m	200 000	Verheyen & Ruyts. 2016
cost of a single mowing on path (€)	C_m	100	Verheyen & Ruyts. 2016
moving frequency on path type (year-1)	F_m	3	Verheyen & Ruyts. 2016

1. The cost of campaign are estimated yearly 2 million instead of calculate the exact cost add up by cost of brochures, leaflet, movies and labour cost, which is hard to calculate because it may be distributed to different stakeholders.

For each intervention, certain assumptions of their effectiveness are made to compare with the basic case. Input parameters were derived from data available for LB in the NL in 2010, published data in 2015 (Table. 2), and expert opinions are described in more detail below and in supplemental materials (Appendix II).

Table 2. Input parameters of the basic case

Parameter	Abbreviation	Distribution and value	Source
Tick bites (2007)	N_0	1,100,00	Hofhuis *et al.*, 2015
LB with EM cases (2014)	N_{LB}	23,500	Hofhuis *et al.*, 2016
Total disease burden in 2010 (DALY)	DALY	1749	van den Wijngaard *et al.*, 2015
Cost of illness in 2010(€)	COI	19.3 million	van den Wijngaard *et al.*, 2017

Basic case

On the basis of available evidence, we assumed the base case scenario, the N_{visit} (number of visiting woods) is 10 million among the 16.6 million population. The N_{TB} (number of LB) is 1.1 million. P_{TB} (possibility of getting tick bites) is assumed as 5% based on the N_{TB} (number of getting tick bites) observed as 1.1 million (Hofhuis et al., 2015).

The P_{inf} (possibility of infected after a tick bites) is calculated as 2% on the basis of available evidence (Sprong & van den Wijngaard. 2016). And finally the N_{LB} (number of LB cases caused by each tick bite in a susceptible population) of LB is 23500 based on the date from 2014 (Hofhuis et al., 2016).

Campaign

The cost of campaign are estimated yearly 2 million instead of calculate the exact cost add up by cost of brochures, leaflet, movies and labour cost, which is hard to calculate because it may happened between different stakeholders. The Ministry of Health, Welfare and Sport (VWS) will invest 2,5 million euros for research into

Lyme disease, assuming the nationwide campaign cost could be simplified into 2 million euro investment.

The effectiveness of campaign was assumed based on a study of students improved their performance markedly after exposure to the leaflet and re-issue of the questionnaire a week later (an increase from 46.1 to 85% and 58.4 to 98.1 % respectively) and improved their performance from 48.2 to 92.8% after a short lecture based on the leaflet contents. Since the nature of human behaviour, the real effectiveness is always lower than expected. The possibility of people going to the woods is assumed -10% because of the fear of getting tick bites. The P_{TB} is decreased by 5% , P_{inf} by 2% and P_{LB} by 1%.

Making signs

The cost of making signs at forest and parks are estimated 16000, which is based on the price of a sign and the amount of signs needed. The effectiveness of a sign was assumed to reduce the P_{TB} by 8% , and by removing the ticks as soon as possible the P_{inf} can be reduced by 3% and the P_{LB} remains the same.

Protective clothing

Wearing a protective clothing properly can prevent more than 99% risk from tick bite. However considering the feasible and willingness, an optimistic estimate of 10% reduction in possibility of getting a tick bites is expected.

Tick repellents

Repellents spray contains 30% DEET is proved to provide a 90% protection against bites (Staub et al., 2002). This indicates using repellents under control is safe for human being as well as effective to keep away from tick and other insects bites. The P_{TB} is estimated to be reduced from 5% to 2%.

The cost calculation model is analyzed and the simulation model of effectiveness are performed by Microsoft Excel and listed in Table 3 and 4.

Mowing vegetation along the path

This intervention will result that the probability of contact with at least one infected tick along a 100m high visitor flow forest trail be reduced from 1 to 0.6 by keeping the density of infected ticks no more than 1/100m^2 (Verheyen& Ruyts, 2016). The cost of mowing 100m length*1m width path is €10 and summed 200 000m length multiplied with 3 times a year. The only parameter it influenced is the P_{TB} and it reduced by 2%.

3. Results

3.1 Selected measures with scientific evidence

Based on the information collected during questionnaire and interview, five measures that help preventing tick bites and LB are selected and defined in this research. A silver bullet for the prevention of LB, such as an efficacious vaccine, is currently not available in Europe, hence prevention predominantly relies on the education of individuals and communities in how to prevent exposure to ticks and therefore tick bites then decrease the risk of LB.

All these measures below are set down in national and international Lyme prevention guidelines. In the Netherlands, there is the multidisciplinary practice guideline on LB by the former Quality Institute for Health Care (CBO), aimed at health professionals involved in the diagnosis, treatment and care of patients suffering from LB. Based on the CBO guideline, there is a guideline for public health care workers produced by the RIVM's National Coordination Centre for Communicable Disease Control (LCI) (CBO 2013, LCI 2016).

1) Public health education and campaign materials for body checking and prompt tick removal and when to visit a physician

The RIVM redesigned the campaign materials for public health education of the general population in 2011, focussed on skin checks and removing ticks - which the public perceived most feasible (Beaujean *et al.,* 2013a), whereas previously the campaign materials presented all possible evidence based preventive measures.

In 2012 the RIVM started approaching the public through social media, and with an educational online video, and school-aged children were targeted with an online serious game, teaching them about ticks and LB in a playful way. Some communication toolkits on prevention of tick bites are available at the ECDC website and at the RIVM website.

Agnetha Hofhuis noted that these measures are relatively easy to achieve but their effectiveness is difficult to measure. The intensified communication and education of toolkits and public health professionals since 2003 have not resulted directly in a decline or even a stabilisation of the incidence of LB in the Netherlands (Hofhuis *et al.,* 2016). The effectivity of the educational online video, online game and the mobile phone app are being evaluated, to be published by Beaujean (Beaujean *et al.,* 2016).

Agnetha said, 'awaiting the study outcomes on effectivity of public health education, we tentatively propose that the decrease in GP consultations for tick bites may reflect the impact of repeated and redesigned efforts of public health education about the relevance of body checking and prompt tick removal and when to visit a physician'. Further monitoring and analysis of the dynamics between humans and Ixodes ricinus (infected with *B. burgdorferi* sensu lato), is required to identify reasons for the currently observed change in trend after 15 years of continuous increase of GP consultations for tick bites and EM diagnoses in the Netherlands (personal communication, 13&14 December 2016).

Rather than developing communication tools for the general public, improvement of the effectiveness might be achieved when at-risk groups for tick bites and LB are specifically addressed with educational tools that fit their perceptions and demands. Selection of such at-risk groups, knowledge on their profiles and an insight into their motives allow health organisations to imply their communication strategies to the characteristics and to make the education more effective.

2) Making signs of the forest to remind:

- **Keep walking in the path at the entrance**
- **Body checking afterwards at the exit**

After visiting areas where ticks could be present, people should check their body for ticks and tick bites. From now on, this will be referred to as doing a 'tick check'. Ticks usually attach themselves to the body on warm places, like in the armpits, in the buttocks, in the knees, under the underwear, behind the ears and around the hairline in the neck (RIVM, 2012). The National Institute for Public Health and Environment explains in a video how a tick can be removed (RIVM, 2012). According to this video, the first step of the tick check is to remove one's clothes to be able to look at the skin. The second step would be to systematically look at one's body from the top to the bottom, paying extra attention to the warm places of the body. For the back or other places one is not able to look at well, a mirror could be used. If a tick is found, it should be removed with pointy tweezers or a tick remover. One needs to grab the head of the tick with the tweezers and pull it out straight. If a tick remover is used, the instructions that come with that remover should be followed. The attachment site should subsequently be disinfected, to prevent cutaneous infection (Pitches 2006). Since ticks do not have a high probability of transmitting *Borrelia* until 12-24 hours after they begin to feed on their host, immediate removal of ticks is one of the most effective ways of avoiding *Borrelia* infection (Beaujean & Sprong, 2016). The sooner a tick is removed from the body, the smaller the chance is to contract LB, and consequently Lyme-related persisting symptoms. For three months after the bite, the site of the bite should be monitored for signs of EM and other possible symptoms. Doing a tick check after visiting nature is thus one of the most important preventive measures to avoid contracting Lyme disease. Also Beaujean *et al.* concluded that public health efforts with regard to Lyme disease should focus on checking for tick bites (Beaujean *et al.*, 2013c).

3) Wearing protective clothing

As mentioned before, people are suggested to wear long, light coloured trousers and to tuck them into their socks to avoid the exposure in tick habitats. In a recent study on effectiveness of personal protective measures to prevent LB, used protective clothing (such as wearing long pants and long-sleeved shirts), while outdoors was 40% effective for preventing LB (Vázquez et al., 2008).

4) Using tick repellents

Using insect repellent that contains permethrin or DEET on clothes or directly on skin offers at least moderate protection against tick bites. The effectiveness was 41.1% (Staub et al., 2002). Kulkarni and Naik evaluated the effectiveness of DEET repellents under laboratory conditions against ticks, the effectiveness was between 80% and 100% against larval, nymphal, and adult ixodid ticks. In a field study, Schreck et al found that a 1-minute application of pressurized sprays of permethrin at 0.5% and DEET at 20% and 30% to the exterior surface of pants and jackets provided 100%, 86%, and 92% protection against bites by all life stages of ticks. From the current study, it appears that under real-life conditions, repellent effectiveness is lower than in laboratory conditions.

Things need to notice are that friction of clothing and other objects; environmental conditions that affect evaporation, such as humidity and physical exercise; absorption from the skin surface; washing by wet vegetation, sweat, or rain; increases in temperature; and exposure to windy environments all reduce repellent effectiveness. Every 10°C increase in air temperature can lead to as much as a 50% reduction in protection time.

5) Regularly grass mowing and leaves removing

Ruyts *et al.* (2016) found a mean density of infected nymphs of 5.9 per 100m^2 in transects laid out within forest stands. Verheyen& Ruyts used a value for contact probability of 1.0 and 0.1 when the vegetation was >50cm and <50cm, respectively.

The value was set followed the seed accessibility factor, for plants with exposed seeds on a stem >30cm. The result shown that the probability of making contact with at least one infected tick along a 100m high visitor flow forest trail can be reduced from 1 to 0.6 by keeping the density of infected ticks no more than 1/100m^2 (Verheyen& Ruyts, 2016).

3.2 Costs of prevention measures

Direct cost and indirect cost are included in the following table of each intervention.

Table 3. Cost estimation of selected measures.

MEASURE	COST (€)	SOURCE
Campaign	2 MILLION	Assumed
Making signs	16000	Online supplier's information
protective clothing	80 million	Arnold van Vliet, personal communication
tick repellents	70 million	Arnold van Vliet, AH.nl
grass mowing	6 million	Verheyen & Ruyts. 2016

Using tick repellents and wearing protective cloth seems to be the two most costly measures from the five. The cost and feasibility of campaign is considered moderate since it is a nationwide programme. It's notable that the money spend on buying repellents and clothes is the public paying instead of the government investment or funding.

3.3 Effectiveness of prevention measures

Table 4. Effectiveness and utility reduction of each measure

	Basic	Campaign	Making signs	Protective clothing	Tick repellents	Mowing
N_0	16600000					
P_{visit}	0,60	0.5(-10%)	0.6(0%)	0.6(0%)	0.6(0%)	0.6(0%)
N_{visit}	10000000	8340000	10000000	10000000	10000000	10000000
P_{TB}	0,11	0.06(-5%)	0.03(-8%)	0.01(-10%)	0.02(-9%)	0.09(-2%)
N_{TB}*	1100000	66000	33000	11 000	20 000	99000
P_{inf}	0,05	0.03(-2%)	0.02(-3%)	0,05(0%)	0,05(0%)	0,05(0%)
N_{inf}	55000	1980	660	550	1100	4950
1-P_{cure}	0,02	0,01(-1%)	0,02(0%)	0,02(0%)	0,02(0%)	0,02(0%)
N_{LB}*	23500	423	282	220	440	1980
DALY*	1749	31,48	20,99	16,37	32,75	147,36
Saved DALY		1717,52	1728,01	1732,63	1716,25	1601,64

*These numbers are derived from the data in Table 2.

In Table 4, all the interventions show a good result in saving DALYs. Protective clothes can be the most favorable measure because it's easy to adopt and providing well protection. Results are sensitive to changes in the probability of reducing risk of getting TB and developing in to LB.

3.4 Cost utility analysis

Table 5. Cost, utility and CUR of each measure, and the potential stakeholder who is going to pay for that

MEASURE	COST (€)	ΔDALY	CUR (€/DALY)	SOURCE OF MONEY
Campaign	2 million	1717,518	1164,47	RIVM & other NGO
Making signs	16000	1728,012	9,26	Private/Government
protective clothing	80 million	1732,626	46172,68	The public
tick repellents	70 million	1716,253	40786,53	The public
grass mowing	6 million	1601,637	3747,65	Private & society cost

Given a certain utility change caused by implement interventions. The smallest CUR is from making signs, while the biggest is protective clothing as shown in

Table 5. According to the calculation, making signs can save per DALY costing only 9.26 euros, which is the most cost—saving . And campaign cost a bit more (€1164,47/DALY) but still cost-effective.

Guidelines for cost-utility of regular health care interventions in Dutch hospitals use up to €50,000 per QALY saved as the maximum cut-off value. For nation-wide prevention programme (e.g. anti-smoking campaigns), the threshold is €20,000 per QALY as the lowest reference value. DALYs and QALYs are technically similar in that they both express health in time (life years) and give a weight to years lived with a disease. So we compare the CUR with the guideline and found, all the CURs of intervention above are lower than the guideline and especially the nationwide campaign are way more lower than the limit €20,000 per DALY.

Since mowing the vegetation has an ecological adverse effect on biodiversity and usually taken action by the owner of the park or forest, this is not a preferable intervention to the societal and environmental aspect.

Making signs at the entrances and exits of woods area is a time and money saving way, which requires a low investment and maintaining fee. At same time it gives an immediate impact then a campaign which could be forgotten after the education.

4. Discussion

Current evidence is unclear and biased

LB risk is magnified when individuals are not aware of the risks, do not mitigate risks, are not familiar with infection signs and symptoms, and do not know where to seek information or support. It is widely accepted that knowledge plays an important role in mediating Lyme disease risk as it is a pivotal precursor to preventative behaviour (Herrington, 2004).

However, in the Netherlands very little is known about the perception and protective behaviour of people in relation to the prevention of tick bites and LB. There is a wide gap between be aware of the risk and taking the action. The medical and scientific communities have been pursuing the problem for years and the public seems to have been well-educated, while, more than 70% of the LB cases happened in the tourism, parks, and outdoor recreation sectors. In 2010 Maat and Konings found in their study (in Dutch) among 600 residents in the southwest of the Netherlands that many respondents lacked skills for recognizing and removing ticks and underestimated their personal risk for tick bites and found protective measures exaggerated(Beaujean *et al.,* 2013a).

In the study on public perceptions and protective behaviours regarding Lyme disease among the general public in the Netherlands by Beaujean *et al.,* 37% of the respondents reported wearing protective clothing when going into nature areas. 32% of the respondents reported checking their skin after they had been outdoors. A minority (6%) reported to use insect repellent skin products (Beaujean et al., 2013a). This percentage is much lower comparing to another American study in which is 75% in average that people used repellent and wore protective clothing (Herrington, 2004).

In fact the amount of people adopting the knowledge to protective behaviours is relatively low. The opinions from RIVM also confirmed this point of view. New prevention strategies should focus on increasing self-efficacy and risk perception.

Many previous studies focused on "taking preventive measures" as one behaviour, while different possible measures should be considered as different behaviours with possibly different determinants. It was concluded that interventions should target the identified determinants of performing a tick check while taking the identified barriers into account. Self-efficacy, also referred as personal efficacy, is the extent or strength of one's belief in one's own ability to complete tasks and reach goals. Arnold van Vliet pointed out that by showing people how to remove the tick properly contribute to the self-efficacy more than simply tell them how dangerous Lyme is (Interview, 19 December 2016).

In the prevention of Lyme disease, every measure is imperfect, we didn't find a silver bullet. Although in our analysis, the DALY reductions of all the measures are high, that's because the assumptions we made about LB prevention measures' effectiveness is high. Because we used a maximum uptake of measures. In reality, however, the uptake is much lower. Our results should tehrefore be seen as maximum effects.

However, it's not certainly included every relevant study in the review, the nature of publication bias makes it unlikely to miss any well-designed studies that described a successful intervention. As the level of research in this field is lacking.

Distribution of costs and benefits

Benefits of better prevention consist of saved DALY's as well as reduced costs of illness. These benefits are taken by the society, however, the costs for prevention are taken by other stakeholders such as the RIVM or landscape management.

From the interview, some stakeholders like Natuurmonumenten think they invest more money in LB than that it costs, by the way of creating posters, providing protective clothes and repellents is the best measurement. However given the workers spend somehow all of their time working outdoors, the potential threat to individual and industry health is cause for concern, while the health outcome is relatively low.

Take the Hoge Veluwe National Park as a representative, which has 7 million euros turnover in 2015. Every year, around 0.6 million visitors, with 3,200 hectares of woodland and 2,100 hectares of heathland, visit the park through 3 entrances. Most people take a white bike at the entrance to cycle along 43 kilometres of cycle path in total. It's not easy for the owner of the park to invest 1 million euros on vegetation mowing. The only real efforts they make is taking care of their employees, by informing them with new knowledge, but also that they can have their blood tested yearly and to have special clothing. Regarding on the visitors, they do think that inform people about the things they think it's necessary knowing but you always miss something and people also have their own responsibility. We cannot expect the green stakeholders to take their responsibility to protect their visitors, but they did well with their employees. So, because the benefits are for society, prevention can be seen as a public task and park owners, therefore, might be subsidized for LB prevention.

Comparison to other economic studies of tick borne diseases

In the US where the vaccine against LB is available, the incremental cost-effectiveness of vaccination was $1,600,000 per case. In the term of CUR is about € 17819/DALY. This number is 10 times higher than implement a nationwide campaign. In this way even vaccine is available in EU, it is not cost-saving for the general population.

Suggestions for future research

Plenty of scope exists for future work to expand this literature and advance our knowledge of how best to encourage members of the public to take protective action when exposed to the risk of tick-borne disease. Future studies could be improved by more field study and human behavior research to determine how the knowledge and perception changes before and after the intervention.

5. Conclusion

Therefore, the main message that can be taken from this analysis is that:

The costs and effectiveness of different preventive interventions are compared to each other. Most cost-saving interventions are placing signs at the entrances and exits of parks and forests. But the effect is largely influenced by human's behaviour. Long-term and promising intervention will be a health education campaign to raise the awareness and self-efficacy of taking the action to avoid tick bites and remove ticks after getting bite.

Improving the uptake of protective behaviours among members of the public is an important challenge for those working to reduce the incidence of tick-borne disease. It is therefore remarkable that so few good-quality studies have assessed the effectiveness of educational interventions in improving this uptake.

Unfortunately, acceptance and uptake of many of these preventive behaviours are currently low. Hence, effective health education and public health communication aimed at promoting the uptake of preventive behaviours regarding tick bites and LB are urgently needed.

Mowing vegetation could be a good way to reduce the amount of ticks and reduce the risk of getting a tick bite, however it has ecological adverse effect on biodiversity.

6. Recommendations

Public health strategies are important in the control of LB, an emerging infection with continually increasing incidence; nonetheless, the implementation and assessment of these strategies have proven to be challenging. Public health officials must take into account not only the effectiveness of the public health strategy, but also the level of engagement of those who are supposed to follow the recommendations. Although this study indicates that use of protective clothing and the use of tick repellents on the skin or clothing while outdoors are effective, clearly not all persons at risk follow these recommendations. Our results provide data to support the policy maker to take better decisions.

Additional educational efforts about these practices, targeted at persons living in LD-endemic areas, may be beneficial. The use of protective clothing may be important for preventing not only LD but also other tick-borne infections. Nevertheless, these strategies, even used optimally, are likely to prevent only a portion of cases of LD. Other strategies, such as mowing the vegetation to reduce tick abundance in areas where human exposure to ticks is high, should continue to be pursued.

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Appendix I Questionnaire

My study is about the economics of Lyme disease prevention and control. This is an interdisciplinary research to illustrate Global One Health approach, financed by strategic research fund in Wageningen.

Currently, there is no quantitative estimation of the cost-effectiveness of Lyme disease prevention and control, while this type of information is necessary for decision makers. This survey aims at getting insight into the point of view from experts about prevention and control measures of Lyme disease.

The interview will take approximately 30 mins. Your sincere opinion is of great value for the success of our study.

Lastly, would you mind me to record the interview? It will only be used in this research. If there are no more questions, let's start.

Introduction question:

1. What's your task with regard to management (prevention and control) of Lyme disease?

List of measures:

2. In your opinion, what do you think is the most cost-utility (cost-effective) measure in the prevention and control of Lyme disease?
3. I made a list of measures that can be implied to manage Lyme disease. (Present the interviewee the list of measures)

   Do you miss any measures or do you disagree with any of these measures? Please add on. (The list can be adjusted after each interview)
4. What are the acceptability of the general public and the willingness of the measures implement?
5. Can you rank the presented measures in the list from high to low effectiveness (by decreasing cases number or percentage) from your expertise?

   And explain the reason that why your ranking (for top 3 and the bottom 3)
6. Can you rank the presented measures in the list from low to high cost (per measure, per year or other unit), from your expertise?

   And give the reason that why you're ranking (for top 3 and the bottom 3)
7. Do you have any remarks, additions or questions concerning this interview or my research? Can I contact you in the future if I have further questions about this topic?

8. Do you want to be informed about the results of this interview?

List of measures

Avoiding Tick Bite

- Avoiding areas with high risk
- Wearing light-colored protective clothing
- Using tick repellants (DEET)
- Frequent body checks for ticks
- Bathing after outdoor activities
- Instituting environmental landscape modifications (e.g., regularly grass mowing, deer exclusion fencing, removing leaf litters and woodpiles)

Remove Ticks

- Remove the tick as quick as possible. Do not wait for it to detach.
- Using fine-tipped tweezers to pull out the tick with the mouth. Don't leave the mouth remaining on your skin.
- Follow up. If you develop a rash or fever within several weeks of removing a tick, see your doctor. Be sure to tell the doctor about your recent tick bite, when the bite occurred, and where you most likely acquired the tick.

Diagnosis and treatment

- Develop into erythema migrans
- Diagnosis testing (ELISA, Western blot)
- Oral regimens (Doxycycline, Amoxicillin)
- Vaccine (not available on market)

Thanks for your time and cooperation! See you.

The list of expertise and stakeholders as a respondent

They are including but not limited to:

Agnetha Hofhuis, epidemiologist, RIVM

Dr. Arnold van Vliet, founder of the teken radar, biologist, WUR

Dr. Hein Sprong, biologist, RIVM

DR. Tim Hofmeeste, disease ecologist, WUR

Jakob Leidekker from de Hoge Veluwe National Park

Stigas, the orgnisation for employees and workers in agricultural and green sectors.

Appendix II Interviews

The answer from different stakeholders colleting during interviews and communication in the conference.

Staatsbosbeheer

I think that giving information is most cost-effective. It's really the best. You can't give people enough information. Repetition is really necessary. I think it really increases the awareness of people. I think that it cheap but has a high effectiveness. Another cost-effective measurement is providing protective clothes to employees. But I think giving information is the best.

RIVM

Giving information and check yourself if you have been to the forest is the cheapest, but not really effective because we do that for years and it is not really helping. The lasts years we put a lot of effort in landscape management, but we didn't find a silver bullet. You can say that that is disappointing, but at least we can now check that off. But I think that all bits and small measurements help, there is not one special measurement. Still, I think that it will be most cost-effective if there is a good diagnostic tests which can take away a lot of the controversy around Lyme disease.

Scouting Nederland

I think that it is cost-effective is you use organisations as ours or other clubs with a lot of members who spend time in nature to spread the information about Lyme disease. We can give this information in our regular messages. Also, it is important that every club has an tick pen and a tick set in their first-aid kit. Also with summer camps and on campsites they can make people aware of ticks and give the people information about the areas with a lot of ticks and that they have to check themselves. Posters and flyers in clubhouses can also increase the awareness because the members are then confronted with Lyme disease. Also, the GGD and general practitioner can create awareness. It also helps if Staatsbosbeheer or other landscape organisations places information signs in the forest or at the roadmap.

GGD

I think that it is most effective to check yourself. That costs nothing and is really effective. I also think that it is cost-effective for employees and other risk groups to wear protective clothes. And I think that people have to seek medical help if they notice symptoms immediately. For example, GP's should give antibiotics immediately if they notice EM. But it is hard to influence GP's because they are very busy and they need to know a lot about so many diseases, so they have to make choices.

Natuurmonumenten

In the prevention of Lyme disease, every measurement is imperfect. Giving information and creating awareness costs nothing except my time and a part of my salary. We do not really know how much the costs of Lyme disease are in this organisations, sometimes employees are sick, but no one has dropped out yet. We spend a lot of time on Lyme and also spend quite a lot of money on it, because we provide protective clothes and repellents. We also create posters. I think that we invest more in Lyme disease than that it costs us. But for our organisations, giving information and providing protective clothes and repellents is the best measurement.

Fieldworker

I think protective clothes, that works. You have less ticks if you wear this clothes. Repellents do not always work, but are cheap. Vaccinations are really expensive to develop, but can be effective if they work. Landscape management is really expensive and is at this moment not really effective. I think that information from organisations as the GGD and the patient association always works. It is not expensive and it is effective for me, because I was bitten by ticks. Before I was bitten by ticks, I did not read flyers and people who are not in contact with ticks will probably throw flyers away, but it does not cost a lot and you can reach a group of people who are in contact with ticks. But protective clothing is one of the best measurement, me and my colleagues really think that it works.