

Prevention interventions for Lyme disease

A systematic review



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December 2017

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Acknowledgements

We would like to acknowledge and give thanks to the patient advocacy group members who attended our consultation sessions and who provided feedback to our survey on the key findings. Participating groups included:- About Time for Lyme, Caudwell LymeCo Charity, Fight Lyme Now, Lyme Disease Action, Lyme Disease UK, VIRAS and Vis-a-Vis Symposiums.

Thanks also go to the members of our scientific advisory group, Public Health England (PHE) and the Department of Health team who provided guidance on the direction of the reviews. We would also like to thank the team undertaking the NICE reviews with whom we worked to ensure synergy between our concurrent programmes of work.

Funding

This is an independent report commissioned and funded by the Policy Research Programme in the Department of Health. The views expressed are not necessarily those of the Department.

Funder involvement

This work is part of an ongoing programme of work funded by the Department of Health (DH) England. Throughout the review, the DH policy team members were consulted to understand the context of the issue under study, collaborated on the development of the research question(s) and informed the focus of the review findings.

Conflicts of interest

There were no conflicts of interest in the writing of this report.

Contributions

The opinions expressed in this publication are not necessarily those of the Department of Health Reviews Facility or the funders. Responsibility for the views expressed remains solely with the authors.

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This report should be cited as:

Richardson M, Khouja C, Walker R, Sutcliffe K, Stansfield C, Harden M, Sowden A, Thomas J (2017). *Prevention interventions for Lyme disease: a systematic review*. London: EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London

ISBN: 978-1-911605-02-7

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Glossary

4-poster device consists of four posts linked together, which apply tick-killing solution to the deer's ears and heads, when they push their heads through to eat the food within the four posts

Acaricide is tick-killing solution

Adjuvant is added to a vaccine to boost the immune response

Antibiotic prophylaxis is taking antibiotics after a tick bite, or other risk, to prevent infection

Babesiosis is an infection spread by ticks (it is not Lyme disease)

Borrelia is a bacterial genus (21/52 species are Lyme disease)

Borreliosis is a disease caused by some *Borrelia* bacteria (Lyme disease)

Borrelia burgdorferi is the Lyme disease spirochete

Borrelia burgdorferi sensu lato is the collection of species causing Lyme disease

Borrelia burgdorferi sensu stricto, *Borrelia afzelii*, and *Borrelia garinii* are the common species that cause Lyme disease in the USA or Europe

B. valaisiana, *B. lusitaniae*, *B. bissettii*, and *B. spielmanii* are a few of the less common species that cause Lyme disease

Confounding variables are factors other than the intervention that could influence the result

Cost-effective means that the cost per effective implementation of the intervention is less than a commonly used or agreed level

Deer cull is killing of all deer in an area

Deer-targeted programmes are deer hunting (reduction in number of deer) and the 4-poster device

Domestic protection involves changes to the landscape (fencing, clearing leaves etc.) or chemical spraying in the garden

Ehrlichiosis is an infection spread by ticks (not Lyme disease)

Erythema migrans is a red ring-shaped rash around a bite, indicating Lyme disease

Exposure days are the number of days spent in the environment where ticks are active

Incidence is the number of new cases in any given period

Matched propensity scores try to eliminate factors that could influence the result

Monovalent vaccine provides protection against only one strain of bacteria

Multivalent vaccine provides protection against many strains of bacteria

Personal protection includes protective clothes and insect repellent applied to the body

Prevalence is the number of cases at any given time

Protective clothes include long trousers (tucked into boots or socks), long-sleeved tops, light-coloured clothes and insecticide-treated clothes

Seronegative has no antibodies (below at a set level) to the disease, in the blood serum

Seropositive has antibodies (above a set level) to the disease, in the blood serum

Tick season describes the months of the year when ticks are active and biting

Abbreviations

AG	Advisory group
ANOVA	Analysis of variance
ARTCA	Anti-recombinant tick calreticulin antibody
CI	Confidence interval
DEET	N,N-Diethyl-meta-toluamide (an insect repellent)
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-Linked Immunosorbent Assay
EM	Erythema migrans
GP	General practitioner
IgG	Immunoglobulin G
NS	Not significant
LDV	Lyme disease vaccine
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OR	Odds ratio
OspA	Outer surface protein A
PHE	Public Health England
PTLD	Post-treatment Lyme disease
RCT	Randomised controlled trial
RR	Relative risk
SE	Standard error
SS	Statistically significant
T1, T2	Time 1, time 2
TBI	Tick-borne illnesses
Td	Tetanus-diphtheria

Executive Summary

Background

Lyme disease is the result of an infection, caused by the *Borrelia burgdorferi* bacterium, which is common in ticks; people can develop Lyme disease after being bitten by an infected tick. This report is one of a series of evidence reviews on Lyme disease, commissioned by the Department of Health (England) Policy Research Programme, and undertaken by the Department of Health Reviews Facility. This evidence review focuses on interventions for preventing Lyme disease. The aim is to determine the types of evaluated interventions, their effectiveness and their applicability to the UK.

Review questions and methods

The review aimed to address the following questions:

- *What types of interventions have been developed to prevent Lyme disease in humans and are they effective?*
- *To what extent are the findings generalisable to the UK context?*

We searched seventeen electronic databases and conducted additional web-based searching for unpublished and grey literature. Empirical research published in or since 2002, on Lyme disease, in humans, was included and synthesised to produce a systematic evidence map that spanned a wide range of topic areas (Stokes et al. 2017). The in-depth review reported herein focuses on evaluations of prevention interventions identified in the map. To be included, studies had to evaluate the effectiveness of an intervention that aimed to reduce the incidence of Lyme disease, in humans, using a control group or comparator research design. Due to the heterogeneity in interventions and outcomes, the data were synthesised narratively and cross-referenced with current prevention guidelines. To see how review findings resonated with UK patient experiences we sought feedback from eight UK patient advocacy groups.

Findings

Eighteen studies were included that evaluated five types of intervention: personal protection (n=4), domestic strategies (encompassing landscape modification and chemical control) (n=3), education (n=6), vaccination (n=5), and deer-targeted programmes (n=2). There were no UK-based studies; 12 were conducted in the USA and six were conducted in Europe. In general, the studies were low in quality and, therefore, had a high potential for bias making it difficult to ascertain reliable information about intervention effects.

Low-quality evidence suggests that personal protection strategies, including the use of tick repellents and wearing of protective clothes, may prevent tick bites among adults.

Low-quality evidence suggests that education interventions may be successful for improving knowledge, behavioural beliefs (e.g., self-efficacy for performing tick checks) and preventative behaviours among adults. The few studies (n=2) that targeted children produced low quality mixed findings for the same outcomes. For both adults and children, changes in beliefs and behaviour did not generally translate into a reduction of tick bites or incidence of Lyme disease.

Whilst the evidence on vaccination of Lyme disease is promising, too few studies were available to reach robust conclusions about effectiveness, and safety.

There was no evidence to support the use of domestic strategies and the culling of deer, and the evidence on the effectiveness of acaricide applied to deer's ears and heads was inconclusive.

Current UK prevention guidance for Lyme disease relates mostly to personal behaviour that aims to prevent tick bites occurring (such as the use of tick repellents and wearing of protective clothes) and is, therefore, consistent with the findings of this review.

Six patient advocacy groups provided feedback on these findings. Three groups felt that a national Lyme disease awareness strategy is needed; two of these groups and one other group suggested that, currently, most awareness raising is undertaken by patient advocacy groups. Two groups expressed concern about the lack of evidence from the UK.

Conclusions

The conclusions must be considered in light of the low quality studies on which they are based. The findings suggest that personal protective strategies that limit exposure to ticks should continue to be recommended, as should education to encourage the adoption of personal protective strategies; further investigation of education interventions for children is particularly needed. Other research needs include:-

- UK-based studies examining the effectiveness of personal protection and education to verify their applicability for this country.
- Evaluations that use objective outcome measures to assess the incidence of Lyme disease (e.g., GP records of diagnoses).
- Empirical work to evaluate the generalisability of these findings to different social and ethnic groups.
- Robust evaluations of antibiotic prophylaxis and checking pets for ticks.
- More research on the effectiveness and safety of vaccination and deer-targeted programmes.
- Collaborative research between key stakeholders to optimise the relevance and utility of Lyme prevention research.

1 Background

This report is one of a series on Lyme disease commissioned by the Department of Health (England) (DH) Policy Research Programme and undertaken by the Department of Health Reviews Facility.

The overarching project consists of a comprehensive evidence map on Lyme disease in humans and four systematic reviews on:-

- 1) the incidence and surveillance of Lyme disease
- 2) patient, clinician and researcher experiences of diagnosis of Lyme disease
- 3) patient, clinician and researcher experiences of treatment and management of Lyme disease
- 4) prevention of Lyme disease

This report details findings from the fourth review on interventions for preventing Lyme disease in humans.

The primary objective of this review is to systematically locate and synthesise the literature on the effectiveness of prevention interventions for Lyme disease in humans to establish a) what types of interventions have been developed and which of these are effective and b) whether and to what extent these findings are generalisable to the UK context.

1.1 Lyme disease

Lyme disease is the result of an infection, caused by the *Borrelia burgdorferi* bacterium¹, which is common in ticks; people can develop Lyme disease after being bitten by an infected tick (Public Health England 2016).

In many cases, an early sign of the infection is erythema migrans or a ‘bull’s-eye’ rash on the skin (Wormser et al. 2006; Stanek and Strle 2003). Clinical complications resulting from Lyme disease include joint, nervous system, and heart problems (Wormser et al. 2006; Stanek et al. 2011, Stanek et al. 2012). In addition, there is some evidence to suggest that presentation is not always ‘typical’ (Bingham et al. 1995; Christen et al. 1993) and that complications may be more wide-ranging and persistent. These persistent complications have been termed chronic Lyme or post-treatment Lyme disease (PTLD) and have been the subject of ‘substantial and polarizing debate’ in the field of medicine for a number of years (Rebman et al. 2017, p. 535).

1.2 The increase of Lyme disease within the UK

Surveillance suggests that the number of cases of Lyme disease is increasing in the UK. Hospital episode statistics report an increase in hospital diagnosis of the condition from 260/year between the years of 2011-2012 to 370/year between the years of 2014-2015 (Cooper et al. 2017), with Public Health England tick surveillance scheme reporting an increase in tick problems in urban areas (Jameson and Medlock 2011). Several reasons for

¹ We refer here to ‘*Borrelia burgdorferi sensu lato*’ which includes all sub-species (including *burgdorferi sensu stricto*, *afzelii*, *garinii*, *mayonii*, *bissettii*, *lusitaniae* and *spielmanii*). We have used the abbreviated phrase in the text for improved accessibility.

the observed increase in Lyme disease in the UK have been suggested, for example an increasing number of deer, the expansion of towns and cities into once-rural land and climate change (Medlock and Leach 2015). This increase in the number of cases of Lyme disease within the UK has called for better knowledge surrounding ways in which the transmission of the disease from ticks to humans can be reduced.

1.3 Preventing Lyme disease in humans

Lyme disease prevention interventions aim to prevent the transmission of the bacterial agent to humans. Suggested strategies include personal protection, such as wearing protective clothing or insect repellent; domestic protection, such as landscape modifications and chemical solutions to reduce tick populations in the garden, educating people on how to avoid being bitten by ticks and how to effectively manage a bite if bitten; and deer-targeted programmes (the primary host of ticks associated with Lyme disease). Vaccines have also been proposed as a preventative strategy; however, available vaccines have been withdrawn due to concerns surrounding adverse reactions and safety (Nigrovic and Thompson 2007). Antibiotic prophylaxis, i.e. the use of antibiotics after a tick bite in order to prevent Lyme disease developing, is a further prevention approach. However, it is currently unknown which interventions are the most effective at preventing infection in human populations.

1.4 Previous research on prevention interventions for Lyme disease

Four systematic reviews were identified in our systematic evidence map (Stokes et al. 2017) that looked at specific aspects of prevention. Warshafsky et al. (2010) examined the treatment effect of antibiotic prophylaxis. The authors concluded that pooled data from four placebo controlled trials supports the use of antibiotic prophylaxis in endemic areas.

Mowbray et al. (2012) examined effectiveness of educational or behavioural interventions for getting members of the public to adopt protective behaviours against tick-borne disease. Interventions that were shown to be effective included one-to-one education by a physician, interactive teaching programmes for children, intensive public educational campaigns, 'shows' and videos that demonstrated the severity of Lyme disease and mailing of information. Nonetheless, seven of the nine included studies had non-randomised designs.

In 2017, two systematic reviews were published that focused on Lyme disease vaccines. Zhao et al. (2017) examined the effectiveness of outer surface protein A (OspA) vaccines (monovalent and multivalent) and concluded that side-effects were rare; therefore this type of vaccine should be considered safe and effective, although further research on improving the vaccine was needed. By contrast, Badawi et al. (2017) conducted a systematic review and meta-analysis of monovalent (LYMErix, ImmuLyme) and multivalent vaccines, and concluded that no currently available vaccine should be recommended because of the risk of harm.

Prevention of disease is far preferable to treating the consequences of tick-borne diseases, therefore, it is essential to understand which strategies are effective. No systematic reviews on personal or domestic protection, or deer interventions, were identified in the evidence map and to our knowledge, no previous evidence synthesis has attempted to systematically review evidence on all types of prevention strategies for reducing Lyme disease in humans, using the most robust methods. Understanding which strategies are most effective can help to shape public policy in the prevention of Lyme

disease and direct investment into the most safe and effective preventative interventions.

2 Aims and methods

This section provides a brief overview of the methods used to conduct the review, sufficient for those primarily interested in the review's findings. A detailed account of the methods, as required for any systematic review, is provided in Section 5.

2.1 Aims

This evidence review focuses on interventions for preventing Lyme disease; its aim is to provide a comprehensive assessment of the evaluated interventions, their effectiveness and their applicability to the UK context.

2.1.1 Review questions

The review aims to address the following questions:

- *What types of interventions have been developed to prevent Lyme disease in humans and are they effective?*²
- *To what extent are the findings generalisable to the UK context?*

2.2 Methods

2.2.1 Study identification

The first phase of the project involved producing a systematic evidence map to cover the whole range of research evidence on Lyme disease in humans (Stokes et al. 2017). We sought relevant studies from within the map for this systematic review.

Details of the strategy and databases searched for the map are provided in Section 5, and an example search strategy is shown in Appendix 1. Full details of the methods and findings of the systematic map are available (Stokes et al. 2017). All studies considered for inclusion in the systematic review were screened independently by two reviewers using the full text.

2.2.2 Inclusion criteria

To be included in the evidence map studies needed to:-

- Be published in or after 2002.
- Be published in the English Language.
- Be about Lyme disease.
- Be an empirical research study OR systematic review.
- Be about Lyme in humans.
- Not be a biomedical study focusing purely on markers or mechanisms of Lyme disease within blood samples, tissue samples, or cells.

To be included in this evidence review, studies also had to:-

- Evaluate the effectiveness of interventions which aimed to reduce the incidence of Lyme disease in humans (i.e., prevention studies).

² The first two research questions detailed in the study protocol are combined in this report.

- Include a control or comparator (of any type).

Further details on these criteria are provided in section 5.

2.2.3 *Data extraction and synthesis*

The included full-text studies were appraised for their quality using the Cochrane Risk of Bias Assessment tool (Higgins et al. 2011) and elements of the ROBINS-I tool for non-randomised designs (see Sterne et al. 2016). One economic evaluation was assessed using a NICE checklist. To generate an overall rating (low, moderate or high risk of bias) for each paper, two questions were examined: is the study sound and is the research design appropriate? For more information, see section 5.1.2 in the detailed Methods chapter, and for the results of the quality assessment for each study see Appendix 4.

A data extraction form was developed and piloted to record the relevant study and participant characteristics, outcome assessments and associated statistical information. Because of the range of included interventions and the heterogeneity of methods, no meta-analysis was conducted, as was originally planned. Data were, therefore, synthesised narratively by intervention type, study design and outcome type.

Between-group effect size estimates for the study outcomes are reported and tabularised (where available), in terms of whether or not the direction of the effect supports the prevention strategy. For example, if greater preventative effects were found in the intervention group, compared with the comparator group, then an effect is said to ‘favour’ the intervention. On the other hand, if greater preventative effects were found in the comparator group, compared with the intervention group, then the preventative intervention is reported to ‘favour’ the control.

Findings at the review level were cross-referenced with the results of the quality appraisal to generate evidence statements for the review. Review findings were then cross-referenced with information on current prevention guidelines in the UK.

Data extraction and quality appraisal tools were initially applied by two reviewers independently until they could be applied with a 90% agreement rate. Data were then extracted by one reviewer and checked by another.

2.2.4 *Consultation with patient advocacy groups*

In October 2017, following the completion of our analyses, we shared the key review findings with eight patient stakeholder groups. The findings were presented as a series of bullet points via an online survey and stakeholder groups were invited to comment.

In addition, we conducted a series of face-to-face consultations with the advocacy groups in July 2017 for our review on experiences of diagnosis (Brunton et al. 2017). Whilst these face-to-face consultations did not require participants to comment on prevention issues directly, several participants raised issues relating to prevention.

Comments relating to Lyme disease prevention, from both of these consultation exercises, are reported in section 3.9.

3 Findings

3.1 Summary of evidence included

- Eighteen evaluations of five types of interventions were included; personal protection (n=4), domestic strategies (n=3), education (n=6), vaccination (n=5), and deer-targeted programmes (n=2)³.
- A range of outcomes was assessed including knowledge, behavioural beliefs, behaviour, incidence of tick bites, and incidence of Lyme infection.
- Eight studies targeted adults⁴, two targeted children, and the remaining eight targeted the general population.
- Nine were randomised controlled trials (RCTs)⁵, three were matched case-control studies, five were observational controlled studies, and one was a cost-effectiveness modelling study.
- Twelve evaluations were conducted in the USA, and six in Europe (Austria, Germany, Sweden, and the Netherlands); thirteen were conducted in a high-risk area, or with participants at a high risk of contracting Lyme disease due to occupational exposure⁶.
- Ten studies reported the gender of participants, ranging from 26% to 65.7% female.
- All but one study was rated as having a high risk of bias.

3.2 Summary of the findings

Table 3.1 provides an overview of the included evaluations. The ‘summary of findings’ column details evidence statements based on a combination of the effectiveness of the interventions and their quality appraisal. Further details of the studies, including participant characteristics (Appendix 3) and results of the quality appraisal (Appendix 4), are provided in the appendices.

Five types of intervention were identified: personal protection (n=4), domestic strategies (n=3), education (n=6), vaccination (n=5), and deer-targeted programmes (n=2). None of the antibiotic prophylaxis interventions, screened at full text, met our study inclusion criteria⁷.

Overall, low-quality evidence suggests that personal prevention strategies, including the use of tick repellents and wearing of protective clothes, may be effective among adults. For adults, low-quality evidence suggests that education methods improved knowledge about Lyme disease, strengthened behavioural beliefs (including self-efficacy for managing

³ Two studies reported both personal and domestic prevention interventions

⁴ One targeted a Military population (assumed to be adults)

⁵ One of which (Shadick et al. 2016) was cluster randomised (by district)

⁶ In addition, one study (Hsia et al. 2002) modelled several levels of risk (incidence of Lyme disease)

⁷ One was not an intervention evaluation but a survey of clinician attitudes/behaviours (Perea et al. 2015); one did not have a control group (Jackson et al. 2014) and two with no useable data (Yagodina 2007; Burdick 2002).

tick bites and, intention to perform tick checks) and increased the frequency of prevention behaviours (including use of repellent and protective clothing), but in terms of reducing tick bites or incidence of Lyme disease the evidence was mixed. For children, the impact of education was inconclusive with two low-quality studies reporting mixed findings for general knowledge outcomes, and checking for ticks. One low-quality education intervention study reported small positive effects for children's self-efficacy in finding a tick on themselves and wearing long pants (trousers), however, there were insufficient data to validate the incidence of Lyme disease (Shadick et al. 2016).

There was no evidence to support domestic strategies, including landscape modifications and chemical solutions (spraying properties), and whilst the evidence for vaccines against Lyme disease is promising, there were too few studies to reach robust conclusions about their efficacy and safety. Furthermore, one low-quality study suggested that vaccination reduced personal protection behaviour and another indicated that vaccination may only be cost-effective when the incidence of Lyme disease is very high.

There was no evidence to support the culling of deer and the evidence on the effectiveness of acaricide applied to a deer's ears and head was inconclusive.

Current UK prevention guidance for Lyme disease relates mostly to personal behaviour that aims to prevent tick bites occurring (such as the use of tick repellents and wearing of protective clothes) and is, therefore, consistent with the findings of this review.

A more detailed narrative synthesis is provided below, which describes the findings by intervention type, study design and outcome. Interventions that target personal and domestic behaviours are described first, followed by education interventions that target these behaviours. Following on from this, non-behavioural interventions are considered, including the efficacy and safety of vaccination for Lyme disease and deer reduction programs.

Box 3.1: How to read and interpret the review findings

To address the first research question (What types of interventions have been developed to prevent Lyme disease in humans and are they effective?), data for each intervention type are reported in sub-sections. For each intervention type, a brief summary of the findings is presented, initially. This is followed by a more in-depth synthesis that details the size of effects, their direction and associated statistical information (see sections 3.3 to 3.7).

For those readers who are less interested in the statistical detail of the findings, the direction of the effects is tabularised (where available), in terms of whether or not the intervention is effective. For example, if greater preventative effects were found in the intervention, compared with the comparator, group then an effect is said to 'favour' the intervention. On the other hand, if greater preventative effects were found in the comparator group, compared with the intervention, then the preventative intervention is reported to 'favour' the control (see Table 3.2 to Table 3.11).

To address the second research question, (To what extent are the findings generalisable to the UK context?) the review findings are cross-referenced with current policy guidelines (see section 3.8 and Table 3.12).

Table 3.1: Summary of the review findings

Intervention type	Outcomes	Relevant studies	Location (risk)	Summary of Results	Type of study
Personal protection	Incidence of Lyme disease	Connally et al. (2009); Vazquez et al. (2008)	USA (high)	Low-quality evidence suggesting the use of tick repellents and wearing of protective clothes may prevent incidence of Lyme disease	2 case-control studies
				Mixed low-quality evidence suggesting tick checks may prevent incidence of Lyme disease	
		Connally et al. (2009)		Low-quality evidence suggesting bathing within two hours of being outside may prevent incidence of Lyme disease	1 case-control study
	Tick measures	Faulde et al. (2015)	Europe (high)	Low-quality evidence suggesting Permethrin-treated battle dress uniform may reduce the frequency of ticks bites	1 historical controlled study
Gardulf et al. (2004)		Europe (high)	Low-quality evidence suggesting the use of Citriodiol insect repellent may reduce the number of ticks crawling or bites	1 RCT	
Domestic strategies: landscape modification and chemical solutions	Incidence of Lyme disease	Connally et al. (2009)	USA (high)	Low-quality evidence suggesting having a fence, having a stone wall, trimming overhanging branches, and having a dry barrier, spraying the yard, and killing other pests may reduce incidence of Lyme Disease	1 case-control study
		Connally et al. (2009); Hinckley et al. (2016); Vazquez et al. (2008)	USA (high)	Low-quality evidence suggesting mowing the lawn frequently, and having a vegetable garden may not reduce incidence of Lyme disease	1 RCT 2 case-control studies
	Tick measures	Hinckley et al. (2016)	USA (high)	Low-quality evidence suggesting that spraying property may not reduce the frequency of ticks crawling or attached. Low-quality evidence suggesting that spraying property may reduce tick density	1 RCT

Education	General knowledge (adults)	Beaujean et al. (2016a)	Europe (general)	Low-quality evidence suggesting that education (leaflet or video, mail, presentation and live show) may increase general knowledge about Lyme disease among adults	3 RCTs, 1 controlled study
		Malouin et al. (2003)	Europe (general)		
		Nolan and Mauer (2006)	USA (high)		
		Daltroy et al. (2007)	USA (high)		
	General knowledge (children)	Beaujean et al. (2016b)	Europe (general)	Low-quality evidence suggesting education (game or leaflet) may be ineffective in improving children's knowledge about Lyme disease (compared with control).	1 RCT
		Shadick et al. (2016)	USA (high)	Low-quality evidence suggesting that education (classroom based sessions) may increase children's knowledge about Lyme disease	1 RCT
	Behavioural beliefs and behaviour (adults)	Beaujean et al. (2016a)	Europe (general)	Low-quality evidence suggesting that education (leaflet or video, live show and mail) may increase behavioural intention of taking preventative measures and efficacy for managing a tick bite among adults	3 RCTs
		Daltroy et al. (2007)	USA (high)		
		Malouin et al. (2003)	USA (high)		
	Behavioural beliefs and behaviour (children)	Shadick et al. (2016)	USA (high)	Low-quality evidence suggesting that education delivered in a classroom setting may increase self-efficacy for tick checking, tick checking and the wearing of long pants among children	1 RCT
		Beaujean et al. (2016b)	Europe (general)	Low-quality evidence suggesting that education (game and leaflet) may be ineffective in reducing tick check frequency among children	1 RCT
	Incidence of Lyme disease (adults)	Daltroy et al. (2007)	USA (high)	Low-quality evidence suggesting that education (live show) may reduce the incidence of Lyme disease	1 RCT
		Malouin et al. (2003)	USA (high)	Low-quality evidence suggesting that postal education may be ineffective in reducing the incidence of Lyme disease	1 RCT
Incidence of Lyme disease (children)	Shadick et al. (2016)	USA (high)	Insufficient evidence to examine effectiveness	1 RCT	

Vaccination	Effectiveness	Wressnigg et al. (2013); Wressnigg et al. (2014)	Europe (general)	Low- and high-quality evidence suggesting that <i>multivalent vaccine</i> may be effective in preventing Lyme disease	2 RCTs
	Safety	Wressnigg et al. (2013); Wressnigg et al. (2014)	Europe (high)	Low- and high-quality evidence suggesting that a <i>multivalent vaccine</i> may be well tolerated	2 RCTs
		Geier and Geier (2002)	USA (general)	Low-quality evidence suggesting increased risk of serious events following use of <i>monovalent LYMERix</i> vaccine	1 retrospective controlled study
	Behaviour	Brewer et al. (2007)	USA (high)	Low-quality evidence suggesting that <i>monovalent LYMERix</i> vaccination may reduce the use of tick repellent, light clothes, long trousers, and tick checks	1 controlled study
	Cost-effectiveness	Hsia et al. (2002)	USA (high and general)	Low-quality evidence suggesting cost-effectiveness of <i>monovalent LYMERix</i> vaccine at incidence of 1% and cost ineffective for US incidence (at 0.0067%)	1 model
Deer-targeted programmes	Tick measures	Jordan et al. (2007)	USA (high)	Low-quality evidence suggesting that deer removal may reduce tick abundance compared with control	1 controlled study
	Incidence of Lyme disease	Garnett et al. (2011)	USA (high)	Mixed low-quality evidence suggesting that 4-poster device may reduce the incidence of Lyme disease Mixed low-quality evidence suggesting that deer removal may reduce the incidence of Lyme disease	1 controlled study

3.3 The effects of personal protection on contact with ticks and incidence of Lyme disease in humans

3.3.1 Summary of the effectiveness of personal protection

The findings for the effectiveness of personal protection strategies on contact with ticks and the incidence of Lyme disease are reported in Table 3.2. The evidence for the use of tick repellents and wearing of protective clothes was consistent across two case-control studies that sampled participants with Lyme disease and matched controls without Lyme disease to ascertain their past preventative behaviour (Connally et al. 2009; Vazquez et al. 2008). Checking for ticks was identified as preventative in Connally's study, but no difference was found in Vazquez's study (possibly due to a longer recall period in Vazquez's study). The positive benefits of tick repellent were verified, in terms of frequency of tick bites, using a RCT (Gardulf et al. 2004). Furthermore, the positive

benefits of permethrin-treated clothing on reducing tick bites were reported in one historical controlled study (Faulde et al. 2015). However, neither Faulde et al. (2015) nor Gardulf et al. (2004) additionally assessed Lyme disease incidence.

3.3.2 *Review synthesis of the effectiveness of personal protection*

Two case-control studies (Connally et al. 2009; Vazquez et al. 2008) sampled the general population in high-risk areas in Connecticut, North America. In a series of logistic regressions, Connally et al. (2009) showed statistically significant differences ($p < 0.05$) favouring prevention between the two groups on tick checks (OR 0.64, 95% CI 0.43 to 0.94), and bathing within two hours of being in the garden (OR 0.60, 95% CI 0.38 to 0.96). Using tick repellent approached statistical significance ($p < 0.1$) and favoured prevention (OR 0.71, 95% CI 0.49 to 1.02). Both the other personal preventative measures, involving the wearing of appropriate clothes, were not statistically significant ($p > 0.20$), but favoured prevention (wearing light-coloured clothes (cases 88% v controls 90%), and long trousers (cases 65% v controls 70%) (ORs not reported).

Vazquez et al. (2008) showed that among definite cases with Lyme disease, two of the three personal behaviours were significantly protective, after adjusting for potential confounders (gender, race, receipt of Lyme vaccine, and the use of other personal protective measures), including wearing protective clothes (OR 0.6, 95% CI 0.5 to 0.7), and the use of tick repellents on skin or clothing (OR 0.8, 95% CI 0.6 to 0.9). Checking the body for ticks was equivalent between groups (77% cases, 77% controls, OR 1.1, 95% CI 0.8 to 1.4)⁸.

Two other studies assessed the effects of personal protection interventions on the incidence of ticks on people (crawling or biting/attached) in high-risk areas but did not include a measure of Lyme disease incidence. Both studies were in Europe; one in Germany (Faulde et al. 2015) and one in Sweden (Gardulf et al. 2004).

Faulde et al. (2015)'s historical controlled study assessed the protective effects of permethrin-treated battle dress uniform, compared with untreated uniform. Bites were reported to a national surveillance system and the follow up involved a questionnaire about the use of the clothing. The 2009 season, before the introduction of treated clothing, was compared with the 2010 and 2011 seasons. In 2009, the bite incidence was 39.3 with 262 bites in 66,679 exposure days, while in 2010 the incidence was 0.16 with 53 bites in 63,571 exposure days (only one bite was with the correct use of the treated clothing). This represented a 1 to 246 reduction ratio or a 99.6% reduction. Similarly, in 2011, there were 18 bites in 17,925 exposure days, with only one being with the correct use of the treated clothes. The reduction ratio was 1 to 71, a 98.6% reduction. Both the mean tick density and the Lyme disease prevalence in ticks remained equivalent from 2009 to 2011, supporting the authors' conclusion that the clothing was very effective, if worn correctly⁹.

⁸ Adjusted for gender, race, receipt of Lyme vaccine, and the use of other personal protective measures

⁹ Incorrect use of the treated clothing was when a mix of treated and untreated clothes were worn or where an untreated parka was worn over the treated clothes.

Gardulf et al. (2004) investigated the effectiveness of lemon eucalyptus extract (Citriodiol), as a repellent to ticks, to prevent Lyme disease. Citriodiol is available, in the UK, in insect repellents, such as Mosi-guard Natural. This randomised controlled trial recruited adults in high-risk areas in Sweden. Participants applied the spray to their legs for two weeks and then crossed over to the control condition (no spray) for two weeks, while controls did the opposite. Spray use was compared with no use, across all participants.

Overall, there were fewer tick bites per person, with the spray, compared with no spray, assessed using the Mann Whitney U test (median 0.5, range 0 to 2 with; median 1.5, range 0 to 9 without; $z = -2.02$, $p < 0.05$) and fewer ticks, that were crawling (not attached) (median 3.5, range 1 to 13 with; median 4.0, range 1 to 20 without; NS). The difference in the number of bites below the waist with Citriodiol, compared with no Citriodiol, was substantial (13 with, 73 without), whereas the difference above the waist (where the spray was not specifically used) was much less but favoured the spray (29 with, 39 without). The relative difference was significant (chi-squared $p < 0.001$). The authors concluded that Citriodiol could be useful for reducing tick bites to prevent infections, such as Lyme disease.

Table 3.2: Summary of findings for personal protection on contact with ticks and incidence of Lyme disease in humans

Study author	Study details	Conditions	Self-reported Behaviour	Evidence of effectiveness
Connally et al. (2009)	Location: High-risk areas in Connecticut, North America Population: General population (aged 1 to 95 years) Sample: 713 Design: Retrospective, case-control study Study period: Interviews conducted within 3 months of diagnosis, recalling the month before EM onset	Cases (physician diagnosed erythema migrans (EM)) and controls (matched for location and age group)	Personal protection	Tick checks and bathing within two hours of being in the garden, favoured prevention ($p < 0.05$). Using tick repellent, wearing light-coloured clothes, and wearing long trousers favoured prevention (NS)
Vazquez et al. (2008)	Location: High-risk areas in Connecticut, North America Population: General population (aged 15 to 70 years) Sample: 1,191 Design: Retrospective case-control study Study period: Interviews conducted within a year of diagnosis, recalling a year before diagnosis	Cases (physician diagnosed EM or tested positive) and control (matched for age and location)	Personal protection	Protective clothes, and insect repellents favoured prevention ($p < 0.05$) Tick checks no difference between intervention and control group (NS)
Faulde et al. (2015)	Location: High-risk areas in Germany, Europe Population: Military personnel (age NR) Sample: 7,151 Design: Historical control Study period: Apr to Sep, 2009 compared with 2010 and 2011	Treated clothing, and non-treated clothing	Ticks attached (bites)	Worn correctly (no non-treated clothes), 98% to 99% reduction in bites

Gar dulf et al. (200 4)	Location: High-risk areas in Sweden, Europe Population: Adults (32 to 78 years) Sample: 111 Design: Crossover randomised controlled trial Study period: Four weeks (two in each condition)	Sprayed repellent (Citriodiol) on legs, did not use repellent	Ticks crawling or attached (bites), and their location	Fewer tick bites (p<0.05) and fewer crawling (NS) favoured prevention
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Note: NS = not statistically significant

3.4 The effects of domestic strategies (including landscape modification and chemical control) on contact with ticks and incidence of Lyme disease in humans

3.4.1 Summary of the effectiveness of domestic strategies

The findings for the effectiveness of domestic prevention strategies are reported in Table 3.3. Data from two case-control studies (Connally et al. 2009; Vazquez et al. 2008) and one RCT (Hinckley et al. 2016) showed little evidence of effectiveness for landscape modifications (various) or chemical solutions, in terms of reducing contact with ticks and incidence of Lyme disease.

3.4.2 Review synthesis of the effectiveness of domestic strategies

In Connally et al. (2009) (that examined high-risk areas in Connecticut, North America), contrary to prevention advice, mowing the lawn three times or more in the last month (OR 1.43, 95% CI 0.97 to 2.11), and having a vegetable garden (OR 1.36, 95% CI 0.97 to 1.91), were risk factors for Lyme disease, at a probability of <0.1¹⁰. Whilst none of the other eight landscape modifications were statistically significant, having a fence (OR 0.79, 95% CI 0.58 to 1.08), having a stone wall (cases 60% v controls 61%, p>0.2), trimming branches near the lawn (cases 83% v controls 85%, p>0.2), and having a dry barrier (cases 12% v controls 16%, p>0.2) were protective. By contrast, the remaining four measures were identified as risk factors for Lyme disease: having a birdfeeder (OR 1.29, 95% CI 0.89 to 1.98), having woods near the property (OR 1.32, 95% CI 0.89 to 1.98), having a log pile (cases 53% v controls 50%, p>0.2, contrary to advice), and clearing leaf litter (cases 54% v controls 46%, p>0.2, contrary to advice).

In the same study, chemical interventions, whilst protective against Lyme disease, were not statistically significant (spraying acaricide in the last two years; cases 10% v controls 12%, p>0.2, and using pesticide for other pests; cases 23% v controls 26%, p>0.2). Similarly, in Vazquez et al. (2008), spraying the property was supported as a prevention strategy, but perhaps due to the sample size (n=16 for case patients and n=52 for matched controls), this did not reach statistical significance (OR 0.6, 95% CI 0.3 to 1.1).

Only one study (Hinckley et al. 2016) assessed the effects of a domestic chemical intervention using a RCT design. In this study, trial households (in high-risk areas in Connecticut, Maryland and New York, North America) received bifenthrin or water, sprayed once on their properties, in the spring. The incidence of ticks found crawling on a

¹⁰ Presumably these equate to time spent in the garden - having a vegetable garden, or frequently mowing the lawn, means that you spend more time in the garden, and are therefore more likely to get Lyme disease.

person was 24.9% of households with treatment, and 27.9% without ($p=0.08$). The incidence of ticks attached was 16.3% with treatment and 17.8% without ($p=0.33$, NS). In terms of the overall nymphal tick density there was a statistically significant difference of 63.4% between acaricide-treated properties (lower density) and control over the two years (overall p -value not reported). For self-reported illness five to six months after intervention, there was no significant difference between households that were sprayed (3.2%) and those that were not sprayed (3.0%; $p=0.78$), and the difference did not favour spraying. Similarly, for illness verified using medical records, there was no significant difference (1.5% with, 1.6% without $p=0.90$), but this difference did (marginally) favour spraying. The authors concluded that acaricide sprayed once as a barrier to ticks, was not significantly effective in reducing tick exposure or incidence of Lyme disease, despite reducing tick density significantly.

Table 3.3: Summary of findings for domestic prevention (including landscape modification and chemical control) on contact with ticks and incidence of Lyme disease in humans

Study author	Study details	Conditions	Self-reported Behaviour	Evidence of effectiveness
Connally et al. (2009)	Location: High-risk areas in Connecticut, North America Population: General population (aged 1 to 95 years) Sample: 713 Design: Retrospective, case-control study Study period: Interviews conducted within 3 months of diagnosis, recalling the month before EM onset	Cases (physician diagnosed EM) and controls (matched for location and age group)	Landscape	Having a fence, having a stone wall, trimming overhanging branches, and having a dry barrier favoured prevention (NS) Mowing the lawn frequently, and having a vegetable garden favoured control ($p<0.1$) Having a bird feeder, woods near the property, having a log pile and clearing leaves favoured control (NS)
			Chemical	Spraying the yard, and killing other pests favoured prevention (NS)
Vazquez et al. (2008)	Location: High-risk areas in Connecticut, North America Population: General population (aged 15 to 70 years) Sample: 1,191 Design: Retrospective case-control study Study period: Interviews conducted within a year of diagnosis, recalling a year before diagnosis	Cases (physician diagnosed EM or tested positive with signs of disseminated disease) and control (matched for age and location)	Chemical	Spraying the property favoured prevention (NS)

Hinckley et al. (2016)	Location: High-risk areas in Connecticut, Maryland and New York, North America Population: Households (adult respondent) Sample: 2,727 households Design: Randomised controlled trial Study period: Surveyed 5 to 6 months after intervention	Property sprayed with acaricide or water (control)	Ticks crawling or attached (bites), and tick density	For ticks crawling or attached, favoured spraying (NS) Tick density lower in acaricide treated properties (SS)
			Self-reported Lyme disease	Favoured control (NS)
			Verified cases of Lyme disease	Favoured spraying (NS)

SS= statistically significant, NS=not statistically significant

3.5 The effects of education interventions on a range of outcomes including knowledge, behavioural beliefs, preventative behaviour and incidence of Lyme disease

3.5.1 Summary of the effectiveness of education

The findings for education are grouped into three sections: impact of education on knowledge (encompassing general knowledge about the disease, knowledge about repellents and acaricide and knowledge about vaccination (summarised in Table 3.7); impact of education on behavioural beliefs (efficacy and intention) and preventative behaviour (various, summarised in Table 3.8); and impact of education on the incidence of Lyme disease (summarised in Table 3.9).

Overall, for adults, education interventions were generally found to be successful for improving knowledge, behavioural beliefs and preventative behaviours (use of repellent, protective clothing and checking for ticks or tick bites), whereas the few studies (n=2) that targeted children produced mixed findings in terms of effectiveness for general knowledge outcomes, and checking for ticks. One study reported small positive effects for children's self-efficacy in finding a tick on their self (Shadick et al. 2016) and wearing long pants in the intervention group versus control. In terms of tick bites and incidence of Lyme disease, mixed findings were reported across two adult-based studies (Malouin et al. 2003; Daltroy et al. 2007) and there were insufficient data to validate the children's reports of Lyme disease in Shadick et al. (2016).

3.5.2 Review synthesis of the effectiveness of education on knowledge outcomes

Six studies were included; five were randomised (Beaujean et al. 2016a; Malouin et al. 2003; Shadick et al. 2016, Daltroy et al. 2007) or cluster-randomised (Beaujean et al. 2016b) controlled trials and one was a controlled (non-randomised) study (Nolan and Mauer 2006). With the exception of two studies which focused on children (Beaujean et al. 2016b, Shadick et al. 2016), the remaining studies targeted adults or the general population.

Beaujean et al. (2016a) conducted a study in the Netherlands to examine the effectiveness of a leaflet and a movie as educational tools for informing the general public about ticks and Lyme disease protective behaviour. Knowledge was assessed immediately post

intervention and at four-week follow-up. As no prior (pre-test) measurements were taken, matched propensity scores¹¹ that controlled for potentially confounding variables were estimated¹².

For clarity and accessibility of text, the effect size estimates (sum scores/fraction of correct answers) by condition and time point, for each knowledge outcome, are shown in Table 3.4. With the exception of recognising initial Lyme disease symptoms (red circle on skin, flu-like symptoms, and painful joints) at follow-up, all measures of knowledge were statistically better in the movie and leaflet groups, compared with control, at both time points (immediately post intervention and four-week follow-up).

With the exception of appropriate health monitoring (which favoured the leaflet condition, albeit not statistically significantly), the knowledge scores favoured the movie (vs leaflet) immediately post intervention ($p < 0.05$) and whilst in the same direction at four-week follow-up, only one (*knowledge of ticks/potential consequences of tick bites*) retained statistical significance ($p < 0.05$). Overall, the results showed that both the movie and the leaflet increased knowledge compared with no treatment control and in general, compared with the leaflet, the movie was more beneficial in improving participant's knowledge about Lyme disease.

Table 3.4: Summary of findings for knowledge outcomes in Beaujean et al. (2016a)

Knowledge outcome	Immediately post intervention			4-week follow-up		
	Movie	Leaflet	Control	Movie	Leaflet	Control
Ticks and the potential consequences of tick bites [sum scores out of 7]	5.41***	5.13***	4.2	4.89***	4.69*	4.45
Preventative behaviour in the case of finding a tick bite on the body [sum scores out of 8]	6.14***	5.77***	4.98	6.07**	5.95*	5.54
Initial Lyme disease symptoms [sum scores out of 6]	5.23***	5.1***	4.78	5.0 ^{NS}	5.0 ^{NS}	5.08
Appropriate health monitoring periods after a tick bite [fraction of correct answers by group]	0.69***	0.74***	0.27	0.5***	0.48***	0.32

¹¹ Propensity scores: based on participant characteristics (age, gender, education, household size, urbanisation category for area of residence, geographic region, daily Internet use, and dog or cat ownership) and potentially influential activities including frequency of walking/running or mountain biking in green spaces, frequency of gardening, frequency of camping, job requiring work in green spaces, tick bite already contracted by self or anyone in direct social network, Lyme disease contracted by self or anyone in direct social network, and previous exposure to the movie or leaflet.

¹² A second control group was recruited at four-week follow-up, to control for possible learning effects. Due to there being no statistical differences between the two control groups, only data for the initial control were discussed.

*p<0.05; **p<0.01; ***p<0.001; NS = not statistically significant; Green shade = direction of effect favoured educational prevention strategy, statistical significance examined using t-test or chi-squared.

Malouin et al. (2003)'s USA-based tick-related prevention programme showed that with the exception of knowing the size of a tick, the intervention led to greater improvement in adult participants' knowledge about Lyme disease (*including attachment time needed for transmission of bacteria, and when to begin protecting self from ticks*), compared with a general health information control. These effects favouring prevention, however, were retained at follow-up for only knowledge about transmission, indicating that general knowledge about tick repellents is challenging to retain and may require booster sessions.

Malouin et al. (2003) also included assessments of knowledge about tick repellents and acaricide. The results for all five measures (summarised in Table 3.5 rather than in-text for clarity) showed greater knowledge improvement among intervention participants who received tick-related education materials bimonthly by post compared with the general health information control group.

Table 3.5: Summary of findings for knowledge outcomes in Malouin et al. (2003)

	Time 2 [June/July 1999]	Time 3 [September/October 1999]
	Odds Ratio >1 favours intervention	
Knowledge about ticks		
Attachment time re: transmission	OR 29.17, 95% CI 10.24 to 83.07**	OR 14.06, 95% CI 5.15 to 38.41**
When one should begin self-protecting from ticks	OR 1.47, 95% CI 0.75 to 2.91 ^{NS}	OR 0.96, 95% CI 0.47 to 1.99 ^{NS}
Knowing the size of the tick	OR 0.69, 95% CI 0.38 to 1.26 ^{NS}	OR 0.52, 95% CI 0.28, 0.95*
Knowledge of tick repellents and acaricide		
Familiarity with the repellent DEET	OR 42.59, 95% CI 15.09 to 120.24**	OR 37.41, 95% CI 12.73 to 109.89**
Knowing the minimum % of DEET needed to be effective	OR 97.67, 95% CI 16.29 to 585.7**	OR 35.23, 95% CI 7.07 to 175.6**
Knowing that DEET is used on the skin	OR 5.41, 95% CI 2.95 to 9.90**	OR 5.43, 95% CI 2.82 to 10.47**
Familiarity with permethrin	OR 36.99, 95% CI 13.60 to 100.63**	OR 36.50, 95% CI 12.15 to 109**
Knowing that permethrin is used on clothing	OR 42.75, 95% CI 14.11 to 129.5**	OR 16.71, 95% CI 5.94 to 47.03**

*p<0.05; **p<0.01; ***p<0.001; NS = not statistically significant; Green shade = direction of effect favoured educational prevention strategy.

Nolan and Mauer (2006)'s non-randomised study examined the effectiveness of two educational modalities before deciding whether to receive a vaccine for Lyme disease: either a face-to-face educational session or a mailed information packet. Various

knowledge outcomes (described in Table 3.6 for clarity) were measured among eligible employees at baseline (autumn 1999, before the education interventions), after administration of the second dose of vaccine (spring of 2000), and after administration of the third dose of vaccine (spring 2001).

Statistically significant results favoured the intervention on all knowledge-based outcomes after administration of the second dose and third dose of vaccine. Chi-squared tests comparing proportions are tabularised by intervention group and time point below.

Table 3.6: Chi-squared tests comparing the proportions for each knowledge outcome in Nolan and Mauer (2006)

Knowledge-based measure	Education session		Mailed Information package		p-value
	n/%		n/%		
	2000	2001	2000	2001	
Knowledge that LDV protects against Lyme disease only	71/88%	61/76%	58/54%	56/55%	p<0.0001 in 2000; p=0.0036 in 2001
Three shots of LDV are required for complete dose	58/72%	62/78%	63/59%	64/63%	p<0.0712 2000; p=0.0401 in 2001
LDV is not 100% effective	64/79%	59/74%	69/64%	61/60%	p<0.0302 in 2000; p=0.0591 in 2001
Duration of protection from LDV is still unknown	58/72%	60/75%	54/50%	51/50%	p<0.0034 in 2000; p=0.0008 in 2001
Preventative activities are still necessary after receiving LDV	77/95%	77/96%	84/79%	84/83%	p<0.0013 in 2000; p=0.0053 in 2001

Green shade = direction of effect favoured educational prevention strategy.

Shadick et al. (2016) evaluated whether a short in-class Lyme disease programme impacted on knowledge among at-risk schoolchildren living in an area highly endemic for Lyme disease (North Shore of Massachusetts). In a randomised study design, change scores pre/post intervention, adjusted for age and gender, were calculated. Overall, *knowledge of Lyme disease* (including how a tick gets on you, whether and when most likely to get sick, how a tick bite can be felt, how a tick can be found, and time taken for Lyme disease to manifest) improved more among children in the intervention (mean improvement = 1.38, SD 1.3), compared with those in the waitlist control (mean improvement = 0.36, SD 1.3) (p<0.0001).

By contrast, however, Beaujean et al. (2016b)'s Netherlands-based study reported no statistical difference between children randomised to an online educational video game or leaflet group *in terms of knowledge about Lyme disease* (tick ecology, basic prevention & tick bites, pooled). Whilst the video outperformed the leaflet (B = 0.735, SE 0.409, p=0.072) the control outperformed the video (B = -0.532; SE 0.33, p=0.112) immediately

post intervention (adjusting for the confounders “knowing somebody with Lyme”, and “having followed classes on tick bites”).

Table 3.7: Summary of findings for education interventions on knowledge outcomes (general, repellents/acaricide, and vaccination)

Study author	Study details	Conditions	Relevant outcome/s	Evidence of effectiveness
Beaujean et al. (2016a)	Location: The Netherlands Population: Adults (aged 18 or over) Sample: 1,677 + 361 at T2 Design: RCT Study period: Post intervention [T1] + 4-week follow-up [T2]	Leaflet, movie, control or follow-up control (recruited at T2)	Knowledge of ticks and the potential consequences of tick bites	Favoured interventions at both time points (SS) Movie better than leaflet at both time points (SS)
			Knowledge of appropriate behaviours in discovery of a tick bite on body within or more than 24h after time spent in green space	Favoured interventions at both time points (SS) Movie better than leaflet at both time points (SS at T1, NS at T2)
			Knowledge of how long to monitor health after a tick bite	Favoured interventions at both time points (SS) Leaflet group outperformed those in the movie group T1 (NS) although the direction was reversed and favoured the movie (modestly) at 4-week follow-up
			Knowledge of initial Lyme disease symptoms (red circle on skin, flu-like symptoms, and painful joints)	Favoured interventions at T1 (SS) Control outperformed both intervention groups at T2 (NS) Movie performed better than leaflet at both time-points (SS at time 1 only)
Malouin et al. (2003)	Location: USA (Baltimore County, Maryland) Population: Adults (18 to 65 years) Sample: 317 Design: RCT Study period: Pre intervention (spring 1999); follow-up 1 (June/July 1999); follow-up 2 (September/October 1999)	Tick-related Education vs general health info	General knowledge about Lyme disease and preventative behaviour	Favoured intervention for knowledge of transmission time at both time-points (SS) Favoured intervention for knowledge of when one should begin self-protecting from ticks at time 1 (NS) but lost at follow-up (NS) Favoured control for knowledge of size of tick at both time-points
			Knowledge of tick repellents and acaricide	Favoured intervention for 5/5 measures at both time points (SS)

Shadick et al. (2016)	Location: USA (North Shore of Massachusetts) area highly endemic for Lyme disease Population: School children (Grades 2 to 5, mean 9.1 years) Sample: 3,570 Design: RCT Study period: Pre/post	Education vs waitlist control	Knowledge of ticks and the potential consequences of tick bites	Favoured intervention (SS)
Beaujean et al. (2016b)	Location: The Netherlands Population: Children (ages 9-13) Sample: 981 Design: Cluster RCT Study period: Pre (Feb-Mar 2012) (t1) /post (Jun-Jul 2012) (t2) intervention	Online video game, leaflet or control	Knowledge (tick ecology, basic prevention & tick bites)	The control outperformed the video and the leaflet conditions (both NS) The video outperformed the leaflet (NS)
Nolan and Mauger (2006)	Location: USA (New York) Population: Adults (21 to 63 years) Sample: 190 Design: Non-randomised controlled Study period: Pre vaccination (autumn 1999); post second dose (spring 2000, T1) and post third dose (spring 2001, T2).	Face-to-face education or a mailed information packet	Knowledge of Lyme disease vaccine (five measures)	Favoured face-to-face education at both time points (all SS)

SS= statistically significant, NS=not statistically significant

3.5.3 Review synthesis of the effectiveness of education on behavioural beliefs and preventative behaviours

Five randomised (Beaujean et al. 2016a; Daltroy et al. 2007; Malouin et al. 2003; Shadick et al. 2016) or cluster-randomised (Beaujean et al. 2016b) controlled trials were included in the synthesis. Two studies focused on children (Beaujean et al. 2016b, Shadick et al. (2016), the remainder targeted adults or the general population. Two studies assessed behavioural beliefs (Beaujean et al. 2016a; Shadick et al. 2016) and all measured behaviour. The results are summarised in Table 3.8 below.

In terms of behavioural beliefs, Beaujean et al. (2016a) included an assessment of efficacy and behavioural intention. Self-efficacy for recognising and managing a tick bite on the skin was higher in the movie (5.48, t-test $p < 0.05$) and leaflet (5.51, t-test $p < 0.01$) conditions compared with the control (5.2), immediately post intervention, adjusting for potential confounding variables. However, at four-week follow-up, whilst the effect remained in the same direction (movie = 5.52, leaflet = 5.56, control = 5.2), the findings did not retain statistical significance. For the response self-efficacy outcome (i.e. the perceived utility that preventative behaviour will help to prevent Lyme disease), whilst both the leaflet (5.49) and movie (5.3) outperformed the control (5.16), only the difference between the leaflet and control obtained statistical significance ($p < 0.001$). While these beneficial effects were maintained at four-week follow-up, the statistical significance was not retained (movie = 5.27, leaflet = 5.4, control = 5.16).

For the behavioural intention of engaging in preventative behaviour, Beaujean et al. (2016a) reported mean comparisons (adjusted for potentially confounding variables)¹³ that showed higher behavioural intention for preventative behaviour in the movie (5.96, $p < 0.01$) and leaflet (5.97, $p < 0.001$) groups, compared with control (5.66), immediately following the intervention. Nonetheless, at four-week follow-up, whilst the direction of the effects remained the same, the statistical significance was not retained (movie = 5.9; leaflet = 5.92; control = 5.85, NS). Interestingly, the leaflet outperformed the movie for measures of efficacy and intention, albeit not statistically. These positive effects for behavioural beliefs, however, did not translate into preventative behaviour (including checking on ticks, tick removal, recording the date and place of tick bite, and visiting a GP) (effect size estimates and statistical tests were not reported).

In Daltroy et al. (2007), ferry passengers (travelling to an endemic area in south-east Massachusetts) were randomised to an educational programme on Lyme disease and other tick-borne illnesses (TBI) or bicycle safety education (control). The results of chi-squared analyses showed that intervention participants were more likely than control participants to take precautions (use repellent, protective clothing, and limit time in tick areas, pooled) against TBI (every day or most days, 58% vs 39%; some days or never, 42% vs 61%; chi-squared $p < 0.0001$) and to check self, daily, for ticks (every day or most days, 51% vs 37%; some days or never, 49% vs 63%; chi-squared $p < 0.0001$) at two-month follow-up.

In Malouin et al. (2003) (discussed above), participants in the intervention group were more likely to have used repellent containing DEET on the skin (OR 6.07, 95% CI 2.74 to 13.42 between spring and summer, 1999; OR 4.40, 95% CI 2.04, 9.48 between summer and autumn, 1999, both $p < 0.01$) and to have used acaricide containing permethrin on clothing, compared with control (OR = 14.22, 95% CI 2.84 to 71.21 between spring and summer, 1999; OR = 11.76, 95% CI 2.40 to 57.68 between summer and autumn, 1999, both $p < 0.01$).

Checking for tick bites was also more common among participants in the intervention group, compared with controls (at both time points), when performed at home (OR 3.18, 95% CI 1.59 to 6.37, $p < 0.01$ between spring and summer, 1999; OR 1.94, 95% CI 0.99 to 3.81, $p = 0.05$, between summer and autumn, 1999). However, when checked away from home, although the direction of the effect supported the intervention condition, statistical significance was not retained (OR 1.37, 95% CI 0.70 to 2.67, $p = 0.35$ between spring and summer, 1999). What's more, between summer and autumn 1999, when checked away from home, the direction of the effect was reversed (favoured control), albeit NS (OR 0.50, 95% CI 0.74 to 3.05, $p = 0.26$). The recommended use of a mirror, held during checking, was also more common among the intervention group, compared with the control group (OR 8.86, 95% CI 3.60 to 21.81 between spring and summer 1999; OR 5.76, 95% CI 2.38 to 13.96, between summer and autumn 1999, both $p < 0.01$).

¹³ Propensity scores: based on participant characteristics (age, gender, education, household size, urbanisation category for area of residence, geographic region, daily Internet use, and dog or cat ownership) and potentially influential activities including frequency of walking/running or mountain biking in green spaces, frequency of gardening, frequency of camping, job requiring work in green spaces, tick bite already contracted by self or anyone in direct social network, Lyme disease contracted by self or anyone in direct social network, and previous exposure to the movie or leaflet.

For children, Shadick et al. (2016) (described above) showed small positive effects for at-risk schoolchildren randomised to a short in-class Lyme disease education programme, for intervention (vs control) in terms of self-efficacy in finding a tick on self (adjusted β 0.07, $p < 0.0001$) and ease/difficulty in checking for ticks (adjusted β 0.16, $p < 0.0001$) immediately post intervention. Following on from this, adjusting for pre-intervention scores and age, intervention children reported checking for ticks (marginally) more frequently than those in the control, post intervention (β 0.06, $p = 0.02$)¹⁴. Relatedly, more students (15% increase) in the intervention group said they checked for ticks behind their ears (β 0.06) and knees (β 0.12) (vs those in the control, both $p < 0.0001$), however, for hand checks, the direction was reversed with a decrease among those in the intervention group (2.8%) and an increase among those in the control group (2.2%) (β -0.06; $p < 0.0001$). Wearing long pants (trousers) was also more common among those in the intervention (vs control) group (β 0.09, $p = 0.002$).

By contrast, Beaujean et al. (2016b) (discussed above) showed that whilst tick checking was more common among children in the video condition, compared with the leaflet (β -0.601, SE 0.291, $p = 0.039$) the video wasn't statistically significantly better than the control (β -0.347, SE 0.298, $p = 0.244$).

Table 3.8: Summary of findings for education interventions on behavioural belief outcomes

Study author	Study details	Conditions	Relevant outcome/s	Evidence of effectiveness
Beaujean et al. (2016a)	Location: The Netherlands Population: Adults (aged 18 years or over) Sample: 1,677 + 361 at T2 Design: RCT Study period: Post intervention [T1] and 4-week follow-up [T2]	Leaflet, movie, control or follow-up control (recruited at T2)	Self-efficacy for recognising and managing a tick bite on the skin	Favoured both interventions at both time points (SS at time 1 only); Leaflet outperformed the movie at both time-points (both NS)
			Response efficacy (belief that preventative behaviours help to prevent Lyme disease)	Favoured both interventions at both time points (SS for leaflet at T1 only) Leaflet outperformed movie at both time points (NS)
			Intention of taking preventative measures	Favoured both intervention groups at both time points (SS at time 1 only) Leaflet outperformed movie (NS)

¹⁴ Betas from linear regression analyses

			Checking on ticks, tick removal, recording date and place of tick bite, and visiting a GP	All NS (effect sizes and statistical tests not reported)
Daltroy et al. (2007)	Location: USA (south-eastern Massachusetts) Population: General (14 to 70+ years) Sample: 30,164 Design: RCT Study period: Pre/two-month follow-up post intervention	Educational programme delivered to ferry passengers and control (bicycle safety education)	Use repellent, protective clothing, limit time in tick areas (pooled)	Favoured intervention (SS)
			Check self, daily, for ticks	Favoured intervention (SS)
Malouin et al. (2003)	Location: USA (Baltimore County, Maryland) Population: Adults (18 to 65 years) Sample: 317 Design: RCT Study period: Pre intervention [spring 1999]; follow-up 1 (June/July 1999); follow-up 2 [September/October 1999]	Tick-related education vs general health info	Checking for tick bites	Favoured intervention at both time points when performed at home (SS)
			Use of a mirror held during checking	Favoured intervention at both time points (SS)
			Used acaricide containing permethrin on clothing	Favoured intervention at both time points (SS)
			Used repellent containing DEET	Favoured intervention at both time points (SS)
Beaujean et al. (2016b)	Location: The Netherlands Population: Children (ages 11 to 13 years) Sample: 981 Design: Cluster RCT Study period: Pre (Feb-Mar 2012) (t1); post (Jun-Jul 2012) (t2) intervention	Online video game, leaflet or control	Tick check frequency	The control outperformed the video and the leaflet conditions (both NS) The video outperformed the leaflet (SS)
Shadick et al. (2016)	Location: USA (North Shore of Massachusetts) Population: School children (Grades 2 to 5, mean 9.1 years) Sample: 3,570 Design: RCT Study period: Pre/post	Education vs waitlist control	Self-efficacy (tick checking)	Favoured intervention (SS)
			Tick checks frequency	Favoured intervention (SS)
			Wearing of long pants (trousers)	Favoured intervention (SS)

SS= statistically significant, NS=not statistically significant

3.5.4 Review synthesis of the effectiveness of education on incidence of tick bite and of Lyme disease in humans

Three studies assessed the incidence of tick bites and Lyme disease. Both of the studies of adults (Malouin et al. 2003, Daltroy et al. 2007) were RCTs, whereas the child-based study (Shadick et al. 2016) employed a pre/two-month-post follow-up controlled design.

In Daltroy et al. (2007) (discussed above), lower rates of tick-borne illnesses (TBI) were self-reported at two-month follow-up (Lyme disease, babesiosis, and ehrlichiosis, pooled) among ferry passengers travelling to Nantucket (an area with a high incidence of Lyme disease) in the education programme versus those in the control group (relative risk [RR] 0.79), though, perhaps due to the low rates of TBI during the study period, statistical significance was not obtained. Nonetheless, a statistically significant interaction for length of stay on Nantucket island by TBI was reported (RR 0.41, 95% CI 0.18 to 0.95, $p < 0.038$). Controlling for covariates¹⁵, these findings showed reduced rates of TBI among the intervention participants (1.58) versus the controls (3.71), when staying for longer than two weeks.

In Malouin et al. (2003), self-reported tick bite was more common in the tick-related educational intervention than the control, at both time points, albeit not statistically significant (OR 0.50, 95% CI 0.19 to 1.27, $p = 0.15$ between spring and summer, 1999; OR 0.37, 95% CI 0.10 to 1.37, $p = 0.14$ between summer and autumn, 1999). A threefold increase in a potential tick-bite bio-marker (known as anti-recombinant tick calreticulin antibody, ARTCA) was observed among three control participants, compared with two participants in the intervention group, though in general there was little variability over time.

In Shadick et al. (2016)'s short in-class Lyme disease education programme, of the 72 parents contacted, only five reported Lyme disease, and only two were confirmed by GP records (one in the intervention group and one in the control group).

Table 3.9: Summary of findings for education interventions on the incidence of tick bites and of Lyme disease in humans

Study author	Study details	Conditions	Relevant outcome/s	Evidence of effectiveness
Daltroy et al. (2007)	Location: USA (south-eastern Massachusetts) Population: General (14 to 70+ years) Sample: 30,164 Design: RCT Study period: Pre/two-month follow-up post intervention	Educational programme delivered to ferry passengers and control (bicycle safety education)	Tick-borne illnesses (inc. Lyme disease, babesiosis, and ehrlichiosis, pooled)	Favoured intervention at two-month (NS) An interaction effect revealed that among those who stayed longer on the island there were fewer incidences of tick-borne illnesses in the intervention vs the control (SS)
Malouin et al. (2003)	Location: USA (Baltimore County, Maryland) Population: Adults (18 to 65 years) Sample: 317 Design: RCT Study period: Pre intervention [spring 1999]; follow-up 1	Tick-related education vs general health info	Self-reported tick bites	Favoured control (NS)
			Anti-recombinant tick calreticulin	Not tested statistically Direction favoured intervention

¹⁵ Age, gender, education, length of time on Nantucket prior to enrolment and post enrolment, time spent in tick areas, permanent residence, and history of Lyme disease or knowing someone with Lyme disease.

	(June/July 1999); follow-up 2 [September/October 1999]		antibody (ARTCA)	
Shadick et al. (2016)	Location: USA (North Shore of Massachusetts) Population: School children (Grades 2 to 5, mean 9.1 years) Sample: 3,570 Design: RCT Study period: Pre/post	Education vs waitlist control	Lyme disease incidence	Insufficient evidence: only five cases of reported Lyme disease, and of these, only two were confirmed by GP records (one each in intervention and control group)

SS= statistically significant, NS=not statistically significant

3.6 The effects of vaccination in terms of effectiveness, safety, risk behaviours and cost-effectiveness

3.6.1 Summary of the effectiveness and safety of vaccination

The findings relating to the effects of vaccination, in terms of effectiveness, safety, risk behaviour and cost-effectiveness are detailed in Table 3.10. Two RCTs (Wressnigg et al. 2013; Wressnigg et al. 2014) reported the effectiveness of a new multivalent vaccine finding that a 30 microgram, adjuvanted dose, given three times, with a booster, was generally effective. However, the long-term effectiveness of the vaccine was not tested and, whilst the vaccine was well tolerated, the trials were small and did not assess long-term outcomes. This multivalent vaccine contains antibodies to six OspA serotypes, protecting against *Borrelia burgdorferi sensu stricto*, *B. afzelii*, *B. garinii*, and *B. bavariensis*, whereas LYMERix (an earlier vaccine withdrawn from the market in 2002) only protected against *B. burgdorferi sensu stricto*. The LYMERix vaccine was shown to have elevated risks of severe adverse effects (Geier and Geier 2002), and reduced preventative behaviour (Brewer et al. (2007). One study showed that the LYMERix vaccine was only cost-effective at high incidence and exposure rates (i.e. for those at a high risk of contracting Lyme disease).

3.6.2 Review synthesis of the effectiveness of vaccination

Two RCTs (Wressnigg et al. 2013; Wressnigg et al. 2014) assessed the effectiveness of a new multivalent vaccine. Both were conducted by the vaccine's manufacturer (Baxter) in Austria and Germany, in people with different serotypes¹⁶.

The 2013 trial (Wressnigg et al. 2013) was a double-blind randomised dose-escalation trial. There were six groups of healthy people, who received doses of 30, 60 or 90 micrograms, with or without adjuvant (1mg aluminium hydroxide per dose). Three doses were given, 28 days apart, followed by a booster at 9 to 12 months. The last follow-up was at 10 to 13 months (one month after the final booster). Whilst all doses and formulations produced a positive response (increased mean IgG antibody titres against OspA serotypes), the highest response after three vaccinations was elicited by the 90 microgram non-adjuvanted formulation.

¹⁶ Seropositive = having antibodies to Lyme disease in their blood serum; or seronegative = with no such antibodies, measured by C6-ELISA (range of Lyme index = 1.10 to 11.47 for seropositive, and 0.03 to 0.90 for seronegative).

After booster, however, the 30 microgram adjuvanted dose produced the highest antibody titres (although between-group statistics were not reported). Compared with baseline, the results among the 30 microgram adjuvanted group ranged from 26,143 (95% CI 18,906 to 36,151) to 42,381 (95% CI 31,288 to 57,407) across the six OspA serotypes. After the booster, 100% (90% CI = 91.3 to 100, n=33) of participants, who received the 30 microgram adjuvanted dose, seroconverted (increased their ELISA titre by four times) and over 80% of participants in this group had OspA titres of at least 10,000 (>1,400 has been proposed to be effective for one season; Van Hoecke et al. 1999). The authors concluded that the new multivalent vaccine could be an effective intervention to prevent Lyme borreliosis in Europe, the USA and worldwide.

The 2014 study (Wressnigg et al. 2014) was a double-blind randomised trial of healthy people who were either seropositive (meaning that their blood tested positive, although they displayed no symptoms) or seronegative (their blood tested negative) for Lyme disease. Participants received three doses of either 30 or 60 micrograms of vaccine with aluminium hydroxide adjuvant (28 days apart), with a booster at either 6 months or 9 to 12 months.

Substantial antibody responses, against all six OspA antigens, were induced after the primary immunisation, in both the seronegative (range 3,799 to 8,543) and seropositive (range 2,413 to 9,435) populations. The antibody responses in the seronegative subjects, induced by the dose formulations (range for 30µg, 3,799 to 6,937, for 60µg, 4,575 to 8,543) were similar (p=0.062). However, in the seropositive subjects, the 60µg dose (range, 4,895 to 9,435) resulted in significantly higher antibody response than the 30µg dose (range, 2,413 to 4,371; p=0.0001).

The booster response was effective at both time points but higher when administered 9 to 12 months after the first immunisation (rather than 6 months, statistics not reported). There were no statistically significant differences in the antibody responses induced, by dose, at 6-month booster (30µg, seronegative range 9,927 to 14,591; seropositive range 10,419 to 15,896; 60µg, seronegative range 11,545 to 18,102; seropositive range 8,064 to 11,167). However, at 9-to-12-month booster, analogous to the situation after primary immunisations, whilst the antibody responses were similar for the two doses among seronegative participants (range, 23,799 to 41,735) with no statistically significant differences among seropositive participants, the 60 microgram dose produced a better response (p=0.0359; for five¹⁷ of the six serotypes, (range 28,735 to 42,381) than for those who received the 30µg dose (range 12,653 to 17,485)¹⁸.

3.6.3 Review synthesis of the safety and cost-effectiveness of vaccination

Three studies assessed vaccine safety. One assessed LYMERix (Geier and Geier 2002) and two assessed the new multivalent vaccine discussed above in the effectiveness section (Wressnigg et al. 2013; Wressnigg et al. 2014) The LYMERix evaluation was conducted in North America, whereas both the new vaccine studies were conducted in Austria and Germany.

¹⁷ Unclear which one was not different, possibly serotype 1

¹⁸ Interestingly, the authors reported a significant effect of age on antibody titre in seronegative (p=0.0067) and seropositive (p=0.0536) participants, but gave no further details.

Geier and Geier (2002) analysed reaction reports within 60 days of receiving the LYMERix vaccine, over 22 months. They compared each incidence with that of the tetanus-diphtheria (Td) vaccination in adults. They also compared the incidence of arthritis between Lyme and rubella vaccines, as rubella has been associated with an increased incidence of arthritis.

There were statistically significant differences (showing more reports of adverse effects with the Lyme vaccine) for the total number of reaction reports (Lyme n=474, Td n=56, relative risk [RR] 8.5), emergency room visits (Lyme n=154, Td n=23, RR 6.7), life-threatening reactions (Lyme n=7.8, Td n=0.46, RR 17), hospitalisations (Lyme n=17, Td n=2.0, RR 8.5), and disabilities (Lyme n=18, Td n=0.28, RR 64) (all $p < 0.0001$). The difference in deaths (Lyme 1.4 v Td 0.06, per million) was not statistically significant.

The differences in alopecia, convulsions and chronic paralysis were not significant. All the other adverse reactions were statistically more common with the Lyme vaccine (at $p < 0.0001$), except lymphadenopathy ($p < 0.0005$). The incidence of these adverse events ranged from 2.1 per million (chronic neuropathy, thrombocytopenia, chronic lymphadenopathy, and chronic gastrointestinal disease) to 64 per million (flu) for Lyme vaccination, and 0.023 per million (chronic gastrointestinal disease) to 2.2 per million (lymphadenopathy) for tetanus-diphtheria vaccination. With the Lyme vaccine, flu was the most common event (64 per million), followed by arthritis (27 per million). Compared with the rubella vaccine, there was a statistically significant increase in arthritis reports (Lyme n=27, rubella n=8.0, RR 3.4, $p < 0.0001$), and chronic arthritis reports (Lyme n=16, rubella n=3.3, RR 4.8, $p < 0.0001$)¹⁹. The overall rate of serious arthritic, neurologic or gastrointestinal reactions, with the Lyme vaccine, was 1 in 8,621 doses. The authors concluded that a safer vaccine was needed.

Wressnigg et al. (2013) assessed adverse events (local and systemic), recorded by participant diary, within seven days of injection. There was a lower risk of systemic adverse reaction (risk ratio = 0.54, 95% CI 0.41 to 0.70; $p < 0.0001$) and of moderate or severe systemic reactions (risk ratio = 0.35, 95% CI 0.13 to 0.92; $p = 0.034$) with the adjuvanted vaccine, compared with non-adjuvanted formulations. The 30µg adjuvanted formulation had the best tolerability profile; only headache (n=5, 10%, 95% CI 4 to 20, of 50), injection site pain (n=16, 32%, 95% CI 21 to 45), and tenderness (n=17, 34%, 95% CI 23 to 47) affected more than 6% of patients. Ten²⁰ serious adverse events were all deemed unrelated to vaccination.

Wressnigg et al. (2014) also assessed local and systemic events within seven days of injection. Across groups, there were local reactions (mostly pain or tenderness) for 58.2% (60 microgram, seronegative) to 63.2% (60 microgram, seropositive) of participants, and systemic reactions (mostly headache, myalgia or fatigue) for 18.4% (60 microgram, seropositive) to 29.7% (30 microgram, seronegative) of participants. No serious vaccine-related adverse events were reported, and there were no symptoms of Lyme borreliosis or chronic arthritis. Three cases of transient arthritis were reported (with the 60 microgram dose). There were no statistically significant differences between seronegative and

¹⁹ A causal relationship has been indicated between the rubella vaccine and both arthritis and chronic arthritis.

²⁰ Bursitis, pulmonary embolism x2, metastasis, lung cancer, cubital tunnel syndrome, ligament rupture, disc protrusion, deep vein thrombosis, and elective abortion.

seropositive groups, either for systemic (RR ranged from 1.09 to 1.13, $p > 0.5862$) or injection site (RR ranged from 1.02 to 1.16, $p > 0.2261$) reactions. There were also no significant differences in reactions overall between doses, across the groups (RR ranged from 0.88 to 1.05, $p = 0.3370$ to 0.9511), and for moderate or severe systemic reactions (RR ranged from 0.97 to 1.11, $p = 0.9054$ to 0.9651). On the basis of the adverse events and antibody titres, the authors identified the 30 microgram adjuvanted dose as the best formulation. They concluded that their vaccine was well tolerated in people who had been infected with Lyme disease.

One study (Brewer et al. 2007) assessed the changes in risk perception and prevention behaviour for Lyme disease in adults who had or had not been vaccinated with LYMERix. Participants were interviewed by telephone before, and 18 months after, vaccination became available.

Interactions between groups (vaccinated vs not vaccinated) by time (baseline and 18 months later) were tested with a repeated measures analysis of variance (ANOVA) controlling for age, gender, education, and race. The results approached, or were, statistically significant for the use of tick repellent ($p < 0.10$) and wearing of light clothes ($p < 0.05$), indicating that those who were vaccinated reduced their prevention more than those who were not vaccinated. Nonetheless, their prevention behaviour remained above that of the non-vaccinated group (means not reported). There were no significant interaction terms for the other three preventative behaviours at follow-up, and, with the exception of avoiding areas of the yard, the behaviours (including wearing long trousers and checking for ticks after being outdoors) reduced more in the vaccinated than in the non-vaccinated group, and for the tick check outcome, dipped below the rate reported for the non-vaccinated group.

One study assessed the effectiveness and cost-effectiveness of vaccination for the prevention of Lyme disease, through the construction of a Markov decision-analysis model, based on probabilities, Lyme disease incidence, and costs estimated from reports in the literature (Hsia et al. 2002). This study was based on the LYMERix vaccine and assessed a hypothetical cohort of people aged 15 to 70 years, living in North America, over ten years.

At the US national average incidence of Lyme disease (0.0067%), and at a cost of \$781.20 for the vaccine, with annual boosters (over ten years), vaccination was not cost-effective (at \$1.6million per case averted, compared with a no-vaccine strategy). As the incidence of Lyme disease increased (1% instead of 0.0067%), this cost reduced to \$9,900 and, with a booster only every three years, it reduced further to \$4,500 (both considered to be cost-effective for the USA). The model showed that the incidence of Lyme disease had to be greater than 10% before vaccination with annual boosters became more clinically effective and cost saving; when a booster was given only every three years, this incidence threshold fell to 5%.

Table 3.10: Summary of findings for vaccination effectiveness, safety, preventative behaviour and cost-effectiveness

Study author	Study details	Conditions	Relevant outcome/s	Evidence of effectiveness
Wressnigg et al. (2013)	Location: Europe (Austria and Germany)	Multivalent vaccine administered	Anti-outer surface protein A (OspA) immunoglobulin G (IgG) antibodies	Whilst all doses and formulations produced a positive response the highest response after three

	<p>Population: Adults (18 to 70 years) Sample: 300 Design: RCT (dose comparison) Study period: Three doses primary immunisation, with a booster at 9 to 12 months. The last follow-up was at 10 to 13 months (one month after the final booster)</p>	<p>ered with or without adjuvant and varied doses: 30, 60 or 90 micrograms</p>	<p>Local or systemic reactions (% of participants)</p>	<p>vaccinations was elicited by the 90 microgram non-adjuvanted formulation The 30 microgram adjuvanted dose produced the highest response after the final booster</p> <p>Reports of systemic reactions were lower in the adjuvanted group, compared with non-adjuvanted formulations. (p<0.0001) The 30µg adjuvanted formulation had the best tolerability profile</p>
Wressnigg et al. (2014)	<p>Location: Europe (Austria and Germany) Population: Adults (18 to 70 years) Sample: 350 Design: RCT (dose comparison) Study period: three-dose primary immunisation boosted by a fourth dose at either 6 months or 9 to 12 months</p>	<p>Multivalent vaccine with adjuvant administered among seropositive or seronegative with varied doses: 30 or 60 micrograms</p>	<p>Anti-outer surface protein A (OspA) immunoglobulin G (IgG) antibodies</p> <p>Local or systemic reactions (% of participants)</p>	<p>Effective among both seronegative and seropositive participants; dose effect among seropositive participants favouring higher (60µg) dose (SS)</p> <p>No statistically significant differences between seronegative and seropositive groups, either for systemic or injection-site reactions. No significant differences in reactions between doses across the groups. The 30 microgram adjuvanted dose was identified as the best formulation</p>
Geier and Geier (2002)	<p>Location: North America Population: Adults (15 to 70 years) Sample: estimated 1.4m doses Lyme disease, 129.3m doses tetanus-diphtheria Design: Controlled (retrospective) Study period: Reports within 60 days of vaccination</p>	<p>Lyme disease (monovalent) vaccine vs tetanus-diphtheria vaccine</p>	<p>Total number of reactions, emergency room visits, life-threatening reactions, hospitalisations, disabilities, and deaths Types of reactions: Arthritis, neuropathy, flu, gastrointestinal disease, convulsions, thrombocytopenia, lymphadenopathy, alopecia, and paralysis</p>	<p>Reactions more common for Lyme vaccine vs tetanus-diphtheria vaccine (p<0.0001) With the exception of deaths, alopecia, convulsions and chronic paralysis, all events increased more in the Lyme vaccine group vs tetanus-diphtheria vaccine</p>
Brewer et al. (2007)	<p>Location: North America (high-risk area) Population: Adults (20 to 70 years, mean 42) Sample: 705</p>	<p>Vaccination (LYMErix) or not vaccinated</p>	<p>Behaviours (tick repellent, light clothes, long trousers, avoid yard, check ticks)</p>	<p>With the exception of avoiding areas of the garden, the prevention behaviours reduced more with vaccination vs no vaccination (wearing of light clothes p<0.05; rest all NS)</p>

	Design: Controlled before-and-after Study period: 18 months			
Hsia et al. 2002	Location: North America Population: Adults (15 to 70 years) Sample: hypothetical cohort 20,000 Design: hypothetical cohort study Study period: 10 years	Vaccination (LYMErix) or not vaccinated	Incidence and cost-effectiveness	At the national average incidence of Lyme disease (0.0067%): not cost-effective compared with no vaccination. At 1% could be considered cost-effective - if willing to pay \$9,900 to avoid a case of Lyme disease Incidence of Lyme disease had to be greater than 10% before vaccination with annual boosters more clinically effective and cost saving (compared with no vaccination)

Note: Seroconverted = increased titre by four times

3.7 The effects of deer-targeted programmes on tick abundance and incidence of Lyme disease in humans

3.7.1 Summary of the effectiveness of deer-targeted programmes

Overall, the results from two before-and-after treatment-control studies indicate that deer culling does not have a positive effect, in terms of reducing tick abundance and incidence of Lyme disease in humans (Jordan et al. 2007; Garnett et al. 2011). The evidence relating to the topical application of acaricide to deer's ears and heads in reducing Lyme disease incidence in humans is inconclusive (as statistically significant positive effects for intervention, compared with control, in the Garnett et al. (2011) study were lost when compared with expanded control areas).

3.7.2 Review synthesis of the effectiveness of deer-targeted programmes

Two studies conducted in North America examined the effects of deer-targeted programmes (Garnett et al. 2011; Jordan et al. 2007). Both had a before-and-after treatment-control design and involved culling of the white-tailed deer (*docoileus virginianus*), which is the primary host of the black-legged tick (*Ixodes scapularis*) that carries Lyme disease.

In Jordan et al. (2007), deer culling was conducted incrementally, commencing in 2002 and was repeated annually (2002, 2003, 2004 and 2005) within the Bernards township area, Somerset County. Surrounding communities (not specified), where deer culling did not occur, were used as control areas. At cull sites the deer population was reduced by 46.7% between the years of 2002 and 2005, from 2,899 (45.6/km²) to 1,540 (24.3/km²). In a series of repeated-measures analyses of variance (ANOVA), mean tick abundance for study years (2002 to 2005) was statistically less compared with the control sites, across life stage of the tick: spring adults²¹ (cull mean ±SE: 1.2±0.2; control mean ±SE: 4.9±0.8,

²¹ The blacklegged tick has different life stages including spring adults, nymphs, larvae and fall (autumn) adults.

$F=16.92$, $p<0.01$), nymphs (cull mean \pm SE: 1.5 ± 0.2 , control mean \pm SE: 2.5 ± 0.2 , $F=13.89$, $p<0.01$), larvae (cull mean \pm SE: 6.7 ± 0.7 , control mean \pm SE: 37.7 ± 6.0 , $F=16.22$, $p<0.01$) and fall (autumn) adults (cull mean \pm SE: 1.5 ± 0.2 , control mean \pm SE: 6.5 ± 0.9 , $F=28.18$, $p<0.01$). Nonetheless, in the culling areas, the number of host-seeking ticks increased during 2002 and 2004, indicating that, overall, there was no decrease in the abundance of ticks due to the removal of deer.

In terms of the incidence of Lyme disease in humans, in the intervention group, rates dropped between the years of 2002 to 2003 ($107.3/100,000$ - $56.6/100,000$) but later increased (to $78.1/100,000$ between 2003 to 2004), indicating no clear trend among study years and that changes in incidence rates could not be attributed to the culling programme.

Furthermore, there was no relationship between deer density and incidence of Lyme disease in humans between 2002 and 2005 ($r=0.68$, $p=0.68$), nor was nymphal tick abundance reported to be a significant predictor of incidence of Lyme disease in humans ($R^2=0.39$, $F=3.91$, $p=0.09$).

Garnett et al. (2011) implemented two deer-targeted interventions, a deer culling (2002) and a four-poster topical treatment device (1997-2002), comparing original treatment and control areas²². For the deer cull, whilst incidence of Lyme disease in humans was reduced at follow-up, the effect was not statistically significant (Mann-Whitney $U=32.5$, $p=0.432$). The relative rates that compared the original treatment / control areas before treatment (relative rate = 13.04), and after treatment (relative rate = 6.99) did not obtain statistical significance (Mann-Whitney $U=30.5$, $p=0.244$). Similarly, the relative rates for the original treatment area/expanded control towns before treatment (relative rate = 2.24) and after treatment (relative rate = 2.38) did not obtain statistical significance (Mann-Whitney $U=38.5$, $p=0.864$).

For the four-poster treatment, results showed that comparing original treatment and control areas, the four-poster topical treatment significantly reduced mean incidence of Lyme disease, in humans, from $427/100,000$ (SD 94.2) between 1992 and 1998 to $137/100,000$ (SD 80.6) between 1999 and 2006 (t-test = 6.35, $p<0.001$).

The relative rate that compared original treatment/control areas before treatment (relative rate=3.93), and after treatment (relative rate=2.38) was statistically significant in the expected direction (Mann-Whitney =74.0, $p=0.040$). Whilst the relative rate reduced post intervention (relative rate=1.36) in the treatment vs the expanded control group compared with before the intervention (relative rate=1.91), the difference was not statistically significant (t-test = 1.54, $p=0.149$)²³.

²² The original treatment area was a four-poster treatment area; the original control area was a similar area in Old Saybrook, Connecticut.

²³ Whilst a measure of tick abundance was not explicitly included, a 71% reduction in nymphal ticks was reported (in the discussion) for the four poster-treatment areas by the 6th year of treatment, however, no between-group comparisons were reported.

Table 3.11: Summary of findings for deer-targeted programmes on ticks and Lyme disease in humans

Author	Study details	Conditions	Relevant outcomes	Evidence of effectiveness
Jordan et al. (2007)	Location: Somerset County, NJ (63.5km ²) Bernards Township (intervention) surrounding control communities Population: General population (age NR) Sample: NA (surveillance data) Design: Before-after treatment control study Study period: 2002-2005	Deer cull	Tick abundance	Favoured intervention (SS) However: overall increase in ticks
			Incidence of Lyme in humans (Physician diagnosed)	No overall decrease Between-group not assessed
Garnett et al. (2011)	Location: South-eastern Connecticut Deer Cull: original treatment cull areas: Mumford Cove, the original control area is the rest of Groton, and the expanded control town is Stonington, Connecticut Population: General population (0 to 92 years) Sample: 2,332 Design: Before-after treatment control study Study period: Deer cull: before 1992-2001; after 2002-2006 Four poster: before 1992-1998; after 1999-2006	Deer cull	Incidence of Lyme in humans (erythema migrans physician diagnosed)	Favoured intervention when compared with original control (NS) favoured control for expanded control group (NS)
		Four poster topical treatment (acaricide applied to deer's ears and heads)		Favoured intervention (SS only when compared with original control, NS for expanded control group)

SS= statistically significant, NS=not statistically significant

3.8 Review findings mapped onto UK policy guidelines for the prevention of Lyme disease

Official guidelines are limited to online material published by Public Health England (PHE), the NHS, the European Centre for Disease Prevention and Control (ECDC) and the National Institute for Health and Care Excellence (NICE). Additional information on practices that take place can be found using other sources, for example, environmental interventions carried out by the Moorland Association. These are detailed in Table 3.12 below alongside the study findings synthesised above.

Concordant with our review findings, which provide consistent evidence for the effectiveness of personal protection interventions (use of tick repellents, wearing protective clothes and tick checks), current UK guidance mostly relates to personal prevention behaviour that aims to prevent tick bites occurring. Consistent with the review findings, this includes promotion of tick checking, the wearing of protective clothing, and the use of repellents and how to safely remove ticks if bitten. Checking pets was also highlighted in the guidance, but did not emerge in our syntheses of prevention studies, indicating a research gap in this field.

There was no guidance located on domestic prevention strategies (including landscape modifications and chemical solutions), which coincides with the lack of peer-reviewed empirical evidence supporting the use of these methods, in our review. In our synthesis of

the evidence, prevention behaviour and associated cognitive antecedents (i.e. knowledge, self-efficacy, and behavioural intention) were targeted using educational interventions that employed a range of methods (including leaflet, video game, postal information, in-class face-to-face sessions, and live entertainment on a ferry journey). These methods support the use of education in effectively modifying behavioural beliefs and preventative behaviour (including use of repellent, protective clothing and checking for ticks) among adults, whereas among children the evidence was mixed, with one study reporting positive effects for knowledge improvement and tick checking and another showing negative effects for these outcomes. For both adults and children there was little evidence that change in beliefs and behaviour led to a reduction in tick bites and Lyme disease.

With the exception of an online training module on Lyme disease for health professionals (The Royal College of GPs), the current educational guidance is didactic in content and delivery consists of published promotional materials on various websites (PHE, NHS, NICE and ECDC), leaflets and posters. By contrast, the synthesis of education interventions revealed that they often contained multiple components including modelling of tick removal (e.g., Daltroy et al. 2007), practice in finding ticks on a rubber arm (Daltroy et al. 2007), feedback (Shadick et al. 2016), social interaction (Shadick et al. 2016), and provision of free materials to support prevention behaviour (e.g., repellent DEET, permethrin, hand-held mirror for tick checking, and tweezers for removing ticks (Malouin et al. 2003).

Two studies provided consistent evidence of effectiveness of a multivalent vaccination in terms of immunogenic response and safety, however more robust, longer term evidence, combined with cost-effectiveness data, is necessary before recommendations can be made. Currently there is no available vaccine against Lyme disease on the market and these findings indicate the potential of vaccination in reducing Lyme disease.

Finally, there was little evidence of the effectiveness of deer culling in our review, and the evidence for the topical application of acaricide to deer's ears and heads was inconclusive as statistically significant positive effects were lost when compared with expanded control areas (Garnett et al. 2011). However, the deer populations on Scottish grouse moors are carefully controlled and moorland sheep are treated (by the moorland association).

Table 3.12: Summary of review findings in relation to guidance on prevention of Lyme disease

Intervention/behaviour	Current guidance	Review findings
Personal protection	Perform tick checks regularly after being outside, check clothes and body, and brush off ticks. Check thoroughly by removing clothing and check children's scalps. Check your pets (PHE, NICE, NHS, ECDC)	Low-quality evidence suggests the <i>use of tick repellents</i> and <i>wearing of protective clothes</i> may prevent incidence of Lyme disease
Domestic prevention (including landscape modifications and chemical solutions)	None located	There was no evidence for domestic strategies including landscape modifications and chemical solutions (spraying properties)

Education	<p>Online materials: Public Health England published promotional material online on tick bite risks and prevention of Lyme disease, including signs and symptoms (PHE, 2013) Information freely available on: NHS, NICE & ECDC websites- includes information on contacting GP if you feel unwell The Royal College of GPs has a training module on Lyme disease, which is free of charge to all health professionals</p> <p>Leaflets and posters: Lyme disease posters, showing how to remove a tick correctly, and leaflets on Lyme disease, are available for publication if required or free of charge for readers to take to their own local GP or veterinary practice</p>	<p>For adults, low-quality evidence suggests that education improved knowledge about Lyme disease strengthened behavioural beliefs (including self-efficacy for managing tick bites and intention to perform tick checks) and increased the frequency of prevention behaviours (including use of repellent and protective clothing) but in terms of reducing tick bites or incidence of Lyme disease the evidence was mixed. For children, the impact of education was inconclusive with two low-quality studies reporting mixed findings. One class-based education intervention reported small positive effects for children’s knowledge and self-efficacy in finding a tick on self and wearing long pants (trousers), however, there were insufficient data to validate the incidence of Lyme disease (Shadick et al. 2016). The other study showed that educational games and leaflet may be ineffective in improving knowledge about Lyme disease and tick checks (Beaujean et al. (2016b))</p>
Vaccination for Lyme disease	Currently no vaccine available to prevent Lyme disease in humans	<p>Whilst the evidence for multivalent vaccination of Lyme disease is promising in terms of effectiveness and safety there were too few studies to reach robust conclusions. Moreover, there is some low-quality evidence to suggest that vaccination reduces personal protection behaviour and is only cost-effective when incidence is high (1%) and cost saving when incidence is very high (10%)</p>
Deer-targeted programmes	<p>The deer populations on Scottish grouse moors are carefully controlled (The Moorland Association) Moorland sheep treated (The Moorland Association)</p>	<p>There was no evidence to support the culling of deer and the effectiveness of acaricide applied to deer’s ears and heads was inconclusive</p>

3.9 Patient advocacy groups' views on these findings

When we asked patient advocacy groups, in October 2017, to comment on the key findings of this review a number of issues were raised by several groups. Three of the eight groups indicated a view that a national strategy for raising awareness of Lyme disease is needed. Three groups felt that most awareness raising is currently undertaken by patient advocacy groups. Two groups expressed concern about the lack of evidence from the UK.

During our face-to-face consultations with groups, in July 2017, several stakeholders commented on the need to raise public awareness, and one noted how a reluctance to openly inform the general public could increase a sense of panic. Another stakeholder indicated the need for detailed evidence on tick removal procedures, to reduce the risk of transmission. Whilst not referring to this review, no evidence on these issues was included in our review, the stakeholder noted that they had seen conflicting research evidence about the timing of tick removal and had found limited detailed information about optimum methods of tick removal²⁴.

²⁴ More extensive patient and public involvement was undertaken, for the review, on the experiences of diagnosis (Brunton et al. 2017).

4 Discussion

The aim of this research review was to locate, synthesise and evaluate intervention studies for the prevention of Lyme disease. The review took a broad focus on interventions that spanned the last 15 years of research (2002 to 2016) and included a total of eighteen studies, six conducted in Europe, and 12 in the USA. There were no UK-based studies. In this final chapter, we summarise the main findings, consider the strengths and limitations, and consider the implications for further research.

Five types of intervention were identified: personal protection (n=4), domestic strategies (n=3), education (n=6), vaccination (n=5), and deer-targeted programmes (n=2). None of the antibiotic prophylaxis interventions, screened at full text, met our study inclusion criteria. Personal protection was the most effective preventative strategy with consistent evidence for the use of tick repellents and wearing protective clothes.

4.1 Personal protection

Mixed findings were reported for the effectiveness of tick checking examined across two low-quality retrospective case control studies comparing participants with and without Lyme disease (Connally et al. 2009 and Vazquez et al. 2008). Bathing within two hours of being in the garden was measured in only one of these studies (Connally et al. 2009) and was shown to support prevention.

Across these same studies, consistent evidence for the use of tick repellents and wearing protective clothes was reported. These findings were corroborated by a study showing that personal prevention methods (permethrin-treated battle dress uniform and insect repellent) reduced frequency of tick bites (Faulde et al. 2015; Gardulf et al. 2004), although neither study additionally assessed the incidence of Lyme disease. Furthermore, the extent to which permethrin-treated clothing provides protective benefits in the general population requires clarification.

4.2 Domestic strategies

There was little evidence of effectiveness for domestic landscape modifications that were assessed in one study (mowing the lawn frequently, having a vegetable garden, having a fence, having a stone wall, trimming branches near the lawn and having a dry barrier, having a birdfeeder having woods near the property, having a log pile and clearing leaf litter), and chemical control solutions (spraying properties), examined in three studies, in reducing tick exposure or incidence of Lyme disease, despite reducing tick density (Connally et al. 2009; Vazquez et al. 2008; Hinckley et al. 2016).

4.3 Education

With the exception of one behaviour identified in the personal protection section above (bathing within two hours of being in the garden), these self-protection behaviours were used to evaluate the effectiveness of the education interventions alongside associated behavioural beliefs (i.e., self-efficacy, and behavioural intention) and knowledge outcomes.

Consistent with previous research (Mowbray et al. 2012), the results suggest that education may modify adults' knowledge about Lyme disease, behavioural beliefs (including efficacy for finding ticks or managing tick bites and intention to engage in

preventative behaviours) and the performance of preventative behaviours (including the use of repellent and the wearing of protective clothing). Nonetheless, only one study additionally reported a reduction in the rate of tick-borne illnesses (pooled), which was enhanced for participants staying longer in the endemic study area, emphasising the importance of long follow-up periods.

There was no evidence of effectiveness for education on a range of preventative behaviours, assessed in one study (including tick removal, recording date and place of tick bite, and visiting a GP), though the absence of evidence does not necessarily imply the absence of effectiveness.

The impact of education about Lyme disease on children was examined less frequently (in two studies only) and produced mixed findings. Positive benefits for Shadick et al. (2016)'s in-class Lyme disease programme were reported for knowledge gains about repellents and acaricide, efficacy for conducting tick checks and frequency of preventative behaviours (including tick checks and wearing of protective clothing). Nonetheless, negative effects on knowledge and tick check frequency were reported for the leaflet and movie methods examined by Beaujean et al. (2016b). These findings imply that learner-centred teaching strategies for Lyme disease, characteristic of Shadick et al. (2016)'s in-class programme, were more effective than the didactic leaflet and movie methods, employed by Beaujean et al. (2016b), though both studies were classified as being low in quality.

Across studies a range of educational methods were examined, including leaflet, video, game, postal information, in-class face-to-face sessions, and live entertainment on a ferry. Furthermore they often contained additional active ingredients besides education, such as modelling of tick removal (e.g., Daltroy et al. 2007), practice in finding ticks on a rubber arm (Daltroy et al. 2007), feedback (Shadick et al. 2016), social interaction (Shadick et al. 2016), and provision of free materials to support prevention behaviour (e.g., repellent DEET, permethrin, hand-held mirror for tick checking, and tweezers for removing ticks; Malouin et al. 2003). This brings into question which of the elements, or combination thereof, are responsible for effectively modifying changes in perception and behaviour, in the context of Lyme disease. Designing an intervention on the basis of the salient mechanisms of behaviour change, with relevant techniques shown to be effective for changing these mechanisms, is likely to improve both the effectiveness of an intervention and understanding about how the intervention works.

4.4 Vaccination

The vaccination studies examined immunogenic effectiveness, safety, risk perception and cost-effectiveness, rather than uptake (as no vaccination is currently, or was at the time, available on the market).

Overall, both company-funded studies reported that their new multivalent vaccine, with adjuvanted dose (that targets more serotypes, making it relevant to the European context, as well as the USA), was effective for the prevention of Lyme disease, with a booster. A significant dose response, among seropositive participants (which favoured a higher dose of 60µg vs 30µg) was reported in one study (Wressnigg et al. 2014), while in another, the 30 microgram adjuvanted dose produced the highest antibody titres (Wressnigg et al. 2013) after the booster. Although the vaccines were well tolerated, follow-up was short (seven days) and sample size was small (n=300 and 350), meaning that they were unlikely to identify any adverse effects that had a frequency of 1 in 8,621

doses, as found in Geier and Geier (2002), who reported statistically significant increases in adverse events with the LYMERix vaccine. Thus, whilst the new multivalent vaccine seems to have slightly lower rates of immediate adverse events, longer term outcomes have not been assessed. Note that the vaccine was voluntarily withdrawn from the market by the manufacturers in 2002, despite approval of the vaccine by the US Food and Drug Administration (FDA). Furthermore one low-quality study (Brewer et al. 2007) indicated that vaccination may reduce preventative behaviour, thus measures of risk perception could, usefully, be included in future work in this area.

The LYMERix vaccination was shown to be cost-effective only at high incidence and exposure rates (i.e. for those at a high risk of contracting Lyme disease). There were no cost-effectiveness studies located for the multivalent vaccine. Overall, while the evidence for the new multivalent vaccine is promising, consistent with Zhao et al. (2017), it is concluded that more robust evidence is needed to guide the development of a future vaccine to prevent Lyme disease in humans.

4.5 Deer-targeted programmes

The deer-targeted interventions examined the effectiveness of reducing tick abundance on a community scale (and as a result the number of bites and incidence of Lyme disease in humans).

Two low-quality studies indicated that deer culling did not have a positive effect, in terms of reducing tick abundance and incidence of Lyme disease in humans (Jordan et al. 2007; Garnett et al. 2011).

The evidence relating to the topical application of acaricide to deer's ears and heads, in reducing Lyme disease incidence in humans, was inconclusive (as statistically significant positive effects for the intervention, compared with control, in the Garnett et al. (2011) study, were lost when compared with expanded control areas).

4.6 Summary

Overall, these findings suggest that personal prevention strategies of tick repellent and wearing protective clothes may be effective. These prevention behaviours may be successfully targeted among adults, using education interventions, but, generally, were not associated with a reduction in tick bites or incidence of Lyme disease. The impact of education on children's perceptions about Lyme disease and their preventative behaviour was inconclusive.

Whilst the evidence for vaccination against Lyme disease is promising, as is the evidence for the topical application of acaricide to deer's ears and heads, further research is needed to examine the effectiveness of these interventions. The extent to which these findings are generalisable to the UK also requires clarification. For example, in regions endemic with Lyme disease, the existing knowledge about Lyme disease may be higher, compared with other regions where Lyme disease is less of an issue or a relatively new problem. Nonetheless, overall these findings are consistent with current UK prevention guidance for Lyme disease, which mostly relates to personal prevention behaviour that aims to prevent tick bites occurring and offers protection against other tick-borne illnesses aside from Lyme disease.

4.7 How do these findings compare with previous research?

These findings are generally consistent with previous reviews discussed in the introduction section (Warshafsky et al. 2010; Mowbray et al. 2012; Zhao et al. 2017). As discussed above, for the educational interventions, our conclusions are consistent with Mowbray et al. (2012), suggesting that educational material could be effective in terms of modifying the knowledge and attitudes and behavioural beliefs in adults. Research published since Mowbray et al. (2012) encompassed interventions that targeted children, however, the findings were mixed and no definitive conclusion could be drawn from the evidence. Despite the inclusion of more studies conducted using a robust study design, study quality was low and uncertainty remains about which educational methods are effective in modifying the knowledge and behaviour of individuals, in the context of Lyme disease prevention. Furthermore, it is still unknown which educational methods, if any, could modify behaviour in such a way that it translates into a reduction in the rate of tick-borne illness.

The findings on vaccination are consistent with a recent systematic review that synthesised the efficacy and safety of vaccines for the prevention of Lyme disease (Zhao et al. 2017), suggesting that the newer multivalent vaccines are effective and well tolerated by users. Nonetheless, due to short follow-up periods, consistent with previous reviews (Zhao et al. 2017), it is concluded that more robust evidence is needed to guide the development of a future vaccine to prevent Lyme disease in humans. This is contrary to Badawi et al. (2017), who concluded in a recent review that no currently available vaccine should be recommended because of the risk of harm.

Whilst no studies assessing the efficacy of antibiotic prophylaxis were eligible for inclusion in the current review, Warshafsky et al. (2010) concluded in their review that the use of antibiotic prophylaxis after an *I. scapularis* bite is effective. However, the use of chemoprophylaxis would need to be considered alongside other factors, such as the potential risks of taking antibiotics and whether the geographical area was disease endemic (Warshafsky et al. 2010).

No systematic reviews were identified that addressed personal protection, domestic strategies or deer-targeting programmes, and to our knowledge, this is the first time that this evidence has been systematically reviewed.

4.8 Strengths and limitations

This is the first systematic review on interventions to prevent Lyme disease that synthesises the findings from a range of interventions. The broad focus and inclusion of controlled studies helped to ensure a comprehensive synthesis of the most robust data available. Nonetheless, none of the included studies were conducted in the UK, and most had a high potential for bias. The majority of the studies relied on self-reporting and, therefore, the findings may be influenced by social desirability, recall bias, and systematic fluctuations in participants' conceptual understanding of outcome assessments. Whilst more high-quality research is needed for reliable conclusions to be reached, the involvement of key stakeholders helped to ensure the relevance of the findings for the UK policy context. Nonetheless, exploration of qualitative data around prevention strategies may elucidate important information, for example, why do people wear, or not wear, repellent, do people know about preventative strategies, and would people be willing to have a vaccine that might have an adverse effect?

Because of the range of included interventions and the heterogeneity of methods, no meta-analysis was conducted, as was originally planned. Consequently, sampling and measurement errors could not be accounted for. Given the range of outcomes and measures, it was not possible to present standardised information about the size of the effects across studies. This points to the lack of shared outcome measures across the included studies. The identification of an agreed set of outcomes would facilitate evidence synthesis and the accumulation of knowledge in this field. In addition, the lack of economic evaluations limits the strength of the evidence regarding the cost implications, and whilst steps were taken to reduce the possibility of publication bias (e.g., searching of relevant websites), we cannot be certain if, and to what extent, publication bias was a problem for these data. Since we only searched for papers published in English, a language bias may also exist. Whilst the scientific advisory group advised inclusion of only the previous 15 years of research (to reflect current experiences and practices relating to Lyme disease), this may have led to potentially useful studies being excluded from the review. Finally, few studies reported information on socioeconomic status and ethnicity, thus the populations, to which these findings generalise, are unclear.

4.9 Implications

- Existing UK guidance that emphasises personal prevention behaviour for Lyme disease, and education to encourage its adoption, should continue to be supported
- UK-based studies examining the effectiveness of personal prevention behaviour and education intervention methods are warranted, given the absence of recent robust UK-based studies in this field
- Evaluations of education about Lyme disease should incorporate objective outcome measures, assessing the incidence of Lyme disease (i.e., GP records of diagnoses), which correspond to the local tick season and employ long follow-up periods
- The impact of education on children's personal preventative behaviour for Lyme disease is unclear and thus warrants further study
- Similarly, more trials to assess the effectiveness and safety of vaccination to prevent Lyme disease and deer-targeted programmes, such as the application of acaricide to a deer's ears and head, are warranted
- Given the absence of recent research on antibiotic prophylaxis and checking pets for ticks, more work in this area is warranted
- Future studies in this area should include demographic assessments, such as social economic status and ethnicity
- Collaboration between key stakeholders, to ensure the relevance and utility of evidence, would help to optimise the research in this field

5 Detailed methods

5.1 Aims

5.1.1 *User involvement*

We worked closely with the review's commissioners throughout, in order to ensure that the review is closely aligned with their needs and emerging programme. In particular, we sought to identify research avenues that would support and complement the evidence being assembled by NICE, in 2017, to produce a guideline for Lyme disease.

We also convened a Scientific Advisory Group (AG) of UK and international academics and UK policy-makers to obtain specialist expertise and input. The AG provided advice on an as-needed basis with regard to technical issues relating to the research questions, concepts and definitions as well as strategies for dissemination and impact. Lastly, we ran a series of consultations with patient and practitioner groups to help interpret our emerging findings in relation to current UK experiences.

5.1.2 *Review questions*

- *What interventions have been developed to prevent Lyme disease in humans and are they effective?*
- *To what extent are the findings generalisable to the UK context?*

5.2 Methods

5.2.1 *Study identification and inclusion in the map*

The first phase of the project involved producing a systematic evidence map covering the whole range of research evidence on Lyme disease in humans (Stokes et al. 2017). The findings of the map were used to populate the subsequent, more focused, systematic evidence reviews, including this fourth review in the series, on prevention methods.

Given the broad scope of the systematic map, the search strategy was sensitive, consisting, in effect, of a single cluster of terms for Lyme disease. The selected databases were identified by members of our team, with extensive expertise in methods for systematic literature searching, including an information specialist. The following databases were searched in August 2016:

ASSIA

British Nursing Index (BNI)

Cochrane Central Register of Controlled Trials (CENTRAL)

Cochrane Database of Systematic Reviews (CDSR)

Cumulative Index for Nursing and Allied Health Literature (CINAHL)

Database of Abstracts of Reviews of Effects (DARE)

Embase

Global Health

Health Management and Information Consortium (HMIC)

Health Technology Assessment (HTA) database

International Bibliography of the Social Sciences (IBSS)

MEDLINE
PsycINFO
PubMed
Social Policy and Practice
Social Science Citation Index
Sociological Abstracts

In addition, the following resources were searched for ongoing studies, and unpublished or grey literature:

ClinicalTrials.gov
Conference Proceedings Citation Index: Science
Conference Proceedings Citation Index: Social Science
EU Clinical Trials Register
ProQuest Dissertations & Theses: UK and Ireland
PROSPERO
WHO International Clinical Trials Registry Platform portal

A search for guidelines on Lyme disease was carried out via the following websites: Health Protection Scotland, Public Health England, Public Health Wales, National Guideline Clearinghouse, NHS Evidence, NICE Clinical Knowledge Summaries (CKS), NICE website and the Trip database.

Further details of the strategy and databases searched are provided in

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Appendices

Appendix 1 and a diagram illustrating the flow of literature through the map and prevention review is provided in Appendix 2.

After the removal of duplicates, 21,174 references were screened on title and abstract; 13,621 were excluded at this stage. Of the remaining 7,553 potential includes, we were able to obtain and re-screen 7,524 full-text papers. At this second stage of screening, 6,440 reports were excluded, of which more than half were published before 2002. This resulted in 1,098 papers that met all inclusion criteria. Of the 82 papers that were identified as prevention studies, 18 were included in the synthesis.

To be included in the evidence map, studies had to meet the criteria set out in

Table 0.1.

Table 0.1: Inclusion criteria for the systematic evidence map

Criterion	To be included in the map a study must:-	Rationale
Date	Be published in or after 2002.	Guidance from members of the scientific advisory group was to focus on recent research from the last 15 years in order to reflect current experiences and practices relating to Lyme disease.
Language	Be published in English Language.	Since the team does not have capacity to search for and examine evidence in all languages we will include only those available in English Language.
Health condition	Be about Lyme disease.	Studies may focus on more than one condition but must include at least some focus on Lyme.
Evidence	Be an empirical research study OR systematic review.	In addition to empirical studies, systematic reviews (i.e. reviews for which ≥ 2 databases were searched and inclusion criteria applied) will be included. Non-empirical evidence, commentary pieces, editorials and non-systematic reviews will be excluded.
Population	Be about Lyme in humans.	Whilst studies of Lyme in animals may provide some information with implications for human populations, the priority is to focus in on those studies directly addressing Lyme in humans.
Focus	Not be a biomedical study focusing purely on markers or mechanisms of Lyme disease within blood samples, tissue samples, or cells.	The aim of the evidence reviews is to understand patient and clinician experiences of Lyme, rather than the underpinning biomedical processes and causative mechanisms, in order to support DH in future policy development.

6.1.1 Screening for inclusion in the prevention review

The full-text screening of potentially relevant articles was carried out by three researchers (MR, CK, RW), using predefined criteria.

To be included, studies had to:

- 1) Evaluate the effectiveness of interventions which aimed to reduce the incidence of Lyme disease in humans.
- 2) Include a control or comparator (of any type).

Pilot screening was initially conducted to ensure that the screening tool was being applied consistently across reviewers (obtaining inter-rater agreement over 90%). All disagreements were resolved by discussion between these researchers.

6.1.2 Number of studies included

A total of 82 full texts were screened. Of these, eighteen met our inclusion criteria and were included in the synthesis.

6.1.3 Data extraction

A data extraction form was developed and piloted to record the relevant study and participant characteristics, outcome assessments and associated statistical information for each evaluation that met the inclusion criteria.

Specifically, the following information was extracted (where reported):

- Country,
- Location (high/low risk for Lyme disease),
- Population (age and gender),
- Sample size,
- Intervention and comparator conditions,
- Study design,
- Study period,
- Delivery format,
- Outcomes (knowledge, behavioural beliefs, personal protection behaviours, domestic strategies, vaccine effectiveness and safety, tick measures, incidence of Lyme disease, and cost-effectiveness), and
- Between-group effect size estimates for the treatment and comparator groups, together with summary statistics and p-values.

Data extraction was initially conducted by three reviewers (MR, CK, RW) who first worked independently, and then checked their work to reach consensus and modify the classification tools until they could be applied with a 90% agreement rate. Data were then extracted by one reviewer and checked by another (shared between MR, CK and RW). The details of study and participant characteristics are provided in Appendix 3.

6.1.4 Synthesis

We had planned to conduct meta-analysis, where feasible, but there were insufficient robust data for meta-analyses. Data were therefore synthesised narratively by intervention type, study design and outcome type, in the first stage. Following on from this, information on current prevention guidelines in the UK was obtained and cross-referenced with the study findings that emerged from stage one of the synthesis.

6.1.5 Quality assessment

The included full-text studies were rated for their methodological rigour and quality using a tool based on the Cochrane Risk of Bias Assessment tool (Higgins et al. 2011). To enable comparison across both randomised and non-randomised designs, elements of the ROBINS-I tool for non-randomised designs (see Sterne et al. 2016, Box 0.1) were incorporated. After a period of pilot screening until an inter-rater agreement of over 90% was obtained, MR independently rated each study. The appraisals were used to evaluate study quality and not to exclude papers.

To generate an overall rating (low, moderate or high risk of bias) for each paper, two questions were examined: is the study sound and is the research design appropriate? Table 0.2 details the criteria for each question (where they deviate from the guidance given in the Cochrane Risk of Bias tool) and it shows how the overall rating for each study was derived. One economic evaluation was assessed using a NICE checklist, see:

<https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-appendix-h-2549711485>. The results of the quality assessment are presented in Appendix 4.

Box 0.1: Quality appraisal questions for evaluations

1. **Was sequence generation random?** (Non-random designs were coded as at high risk of bias)
2. **Was allocation concealment of randomisation reported?** (pre/post observational studies were coded as being at high risk of bias)
3. **Was there baseline equivalence?** (unclear if insufficient evidence e.g. a full table of participant characteristics for each group, was not reported)
4. **Was there blinding of participants and researchers?** (In relation to those who received the intervention or the control)
5. **Was there blinding of outcome assessment** (knowledge of whether data came from intervention or control)
6. **Was there incomplete outcome data** (acceptably low if <20% overall and <10% difference between groups. Studies which adjusted for imbalances in attrition in the analysis were also considered as at low risk of bias)
7. **Selective reporting** (were all important benefits and harms measured, and were all the reported measures assessed?)
8. **Was there any other risk to bias** (use of validated tools and inter- or intra-rater reliability was assessed)

Table 0.2: Overall rating of risk of bias

Risk of bias criterion	Effectiveness Synthesis
Is the study sound?	A study was rated as sound if: <ol style="list-style-type: none"> i. The two comparators (intervention and control group) were equivalent ii. Blinding of outcome assessment iii. There was no evidence of a substantial amount of attrition from the study or differential rates of attrition between the two groups (cluster RCTs, RCTs and non-RCTs only)
Is the research design appropriate?	Research designs were rated as: <ul style="list-style-type: none"> • Gold Standard - RCT • Highly appropriate - non-RCT • Moderately appropriate -pre/post observational study
What is the overall risk of bias?	<p>Low risk of bias = Sound studies employing gold standard or highly appropriate research design</p> <p>Moderate risk of bias = Sound studies employing moderately appropriate research design</p> <p>High risk of bias = Any study that is not sound</p>

6.1.6 Consultation on key findings with patient advocacy groups

In October 2017, following the completion of our analyses, we shared the key findings with eight patient stakeholder groups. The findings were presented as a series of bullet points via an online survey and stakeholder groups were invited to comment. We requested that each group provide a single collated response for their group. As one group was unable to

meet this request we had a member of the research team who was not involved in writing up the consultation findings collate the response for this group. The collated responses for each group were then assessed to check whether the key findings resonated or not with patient groups own experiences.

In addition, we conducted a series of face-to-face consultations with the advocacy groups in July 2017 for our review on experiences of diagnosis; for further details on the methods for these consultations see Brunton et al. (2017). Whilst we did not directly ask participants to comment on prevention issues during the face-to-face consultations, several participants did raise issues relating to prevention.

Comments relating to Lyme disease prevention, from both of these consultation exercises, are reported in section 3.9.

7 References

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Appendices

Appendix 1: Sample search strategy: MEDLINE (via Ovid) search strategy

- 1 exp Lyme Disease/ (9589)
- 2 (lyme or lymes or lyme's).ti,ab. (9797)
- 3 borreliosis.ti,ab. (3230)
- 4 neuroborreliosis.ti,ab. (1024)
- 5 (borrelia\$ adj2 arthritis).ti,ab. (38)
- 6 (erythema adj2 migrans).ti,ab. (1471)
- 7 1 or 2 or 3 or 4 or 5 or 6 (12593)
- 8 exp Borrelia burgdorferi Group/ (6501)
- 9 (borrelia adj (burgdorferi or afzelii or garinii)).ti,ab. (7347)
- 10 (b adj (burgdorferi or afzelii or garinii)).ti,ab. (4289)
- 11 8 or 9 or 10 (8983)
- 12 7 or 11 (14245)
- 13 exp animals/ not humans/ (4279323)
- 14 12 not 13 (11450)

The following databases were searched:

ASSIA

British Nursing Index (BNI)

Cochrane Central Register of Controlled Trials (CENTRAL)

Cochrane Database of Systematic Reviews (CDSR)

Cumulative Index for Nursing and Allied Health Literature (CINAHL)

Database of Abstracts of Reviews of Effects (DARE)

Embase

Global Health

Health Management and Information Consortium (HMIC)

Health Technology Assessment (HTA) database

International Bibliography of the Social Sciences (IBSS)

MEDLINE

PsycINFO

PubMed

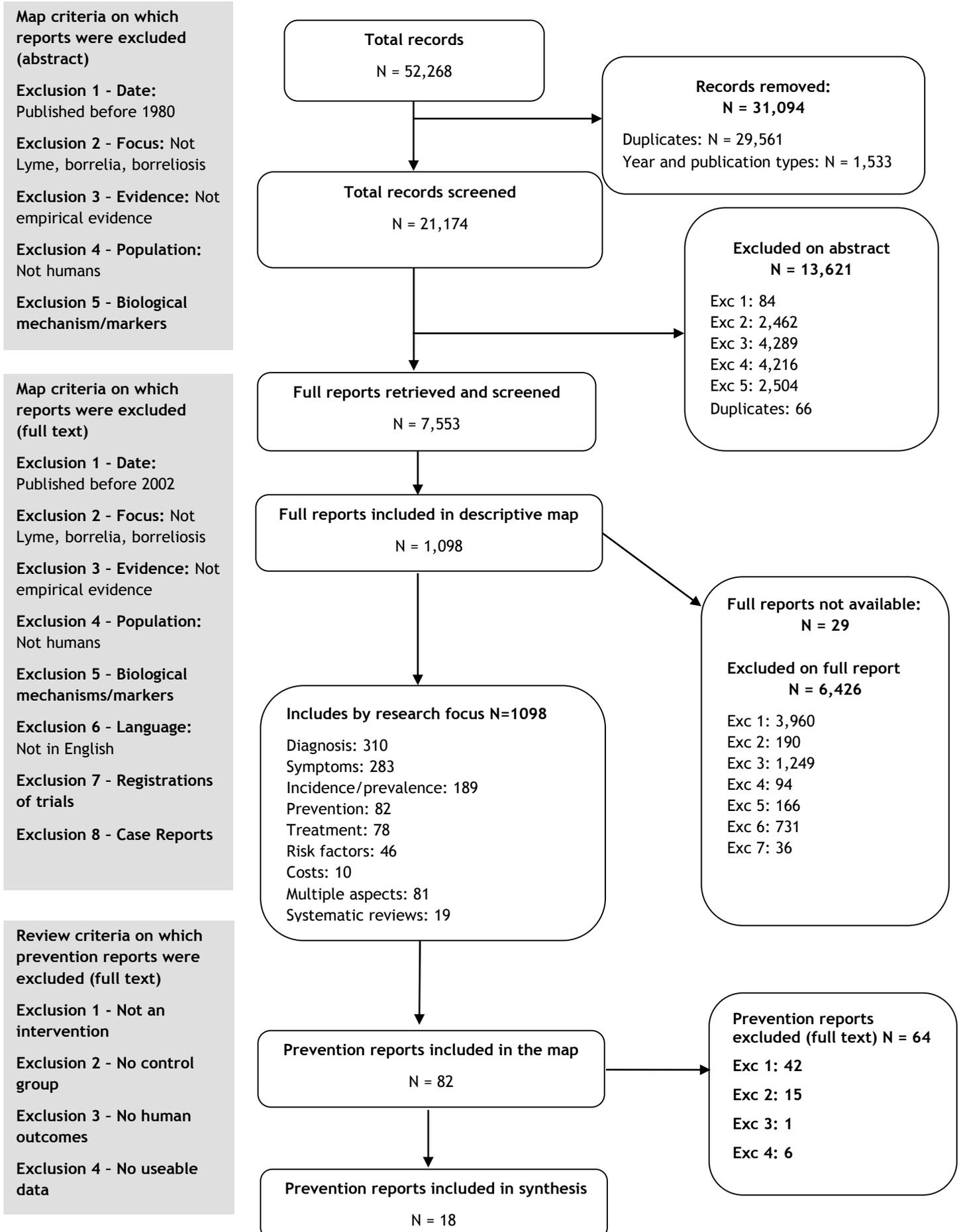
Social Policy and Practice
Social Science Citation Index
Sociological Abstracts

In addition, the following resources were searched for on-going studies, unpublished or grey literature:

ClinicalTrials.gov
Conference Proceedings Citation Index: Science
Conference Proceedings Citation Index: Social Science
EU Clinical Trials Register
ProQuest Dissertations & Theses: UK and Ireland
PROSPERO
WHO International Clinical Trials Registry Platform portal

A search for guidelines on Lyme disease was carried out via the following websites: Health Protection Scotland, Public Health England, Public Health Wales, National Guideline Clearinghouse, NHS Evidence, NICE Clinical Knowledge Summaries (CKS), NICE website and the Trip database.

Appendix 2: Flow of literature through the map and review



Appendix 3: Study details

Study	Intervention	Country	Population	Sample size	Design	Conditions	Delivery and follow-ups	Outcomes
Beaujean et al. (2016a)	Education	Europe (Netherlands)	Age: Adults (18 years +) % Female: Movie 53.4%, Leaflet 56.9%, Control1 56.7%, Control2 51.5%	1,677 +361 at Time 2	RCT	Leaflet, movie or no treatment control	Delivery: Online Follow-up: One month	Knowledge, Behavioural beliefs, Behaviour
Beaujean et al. (2016b)	Education	Europe (Netherlands)	Age: Children (11 to 13 years) % Female: NR	981	RCT cluster	Game, leaflet, or no treatment control	Delivery: Online game or leaflet Follow-up: 4 months approx.	Knowledge, and behaviour
Brewer et al. (2007)	Vaccination	North America (Northeast)	Age: Adults (20 to 70 years) % Female: 60%	705	Controlled	LYMErix vs No vaccine	Delivery: NA Follow-up: Recall period not reported	Behaviour
Connally et al. (2009)	Personal protection + Domestic strategies	North America (Connecticut)	Age: General population (1 to 95 years) % Female: NR	713	Retrospective case-control	Participants with and without previous incidence of Lyme disease	Delivery: NA Follow-up: recalled 1 month before erythema migrans onset	Personal protection and domestic strategies
Daltroy et al. (2007)	Education	North America (Nantucket Island, MA)	Age: General population (14 to 70+ years) % Female:	30,164	RCT	Lyme disease education vs bicycle safety information (Live show)	Delivery: Face-to-face Follow-up: Two months	Knowledge, Behaviour Incidence of Lyme disease

			Intervention 57.4%, Control 59.8%					
Faulde et al. (2015)	Personal protection	Europe (Germany)	Age: Military personnel (age NR) % Female: NR	7,151	Controlled	Permethrin treated battle uniform vs non treated uniform	Delivery: NA Follow-up: Apr to Sep, 2009 was compared with 2010 and 2011	Tick measures (incidence of bites)
Gardulf et al. (2004)	Personal protection	Europe (Sweden)	Age: Adults (32 to 78 years) % Female: 60.3%	111	RCT (cross-over)	Citriodiol repellent vs no treatment	Delivery: NA Follow-up: Four weeks (two in each condition)	Tick measures (Incidence of bites/ ticks crawling)
Garnett et al. (2011)	Deer reduction	North America (SE Connecticut)	Age: General population (0 to 92 years) % Female: NR	2,332	Controlled	4 poster device (acaricide applied to deer's ears and head) or deer removal in treatment towns vs no treatment control towns	Delivery: NA Follow-up: Deer cull: before treatment 1992-2001; after 2002-2006; Four poster: before treatment 1992-1998; after 1999-2006	Incidence of Lyme disease
Geier and Geier (2002)	Vaccination	North America	Age: General population (15 to 70 years) % Female: NR	Lyme disease: 1,400,000 doses, Td ²⁵ : 129,293,354 doses (both estimated)	Controlled (retrospective)	LYMERix vs tetanus-diphtheria vaccine	Delivery: NA Follow-up: Reports within 60 days of vaccination	Vaccine safety

²⁵ Td = tetanus-diphtheria vaccination

Hinckley et al. (2016)	Domestic strategies	North America (Connecticut, Maryland, and New York)	Age: General population % Female: NR	2,727 households	RCT	Acaricide vs placebo	Delivery: Trained, licensed pest control operators Follow-up: 5 to 6 months	Incidence of Lyme disease, tick measures (incidence of bites/ticks crawling)
Hsia et al. (2002)	Vaccination	North America	Age: General population (15 to 70 years) % Female: NR	Hypothetical cohort of 20,000 people	Modelling-based study	LYMERix vaccinated or not	Delivery: NA Follow-up: ten-year study period	Cost-effectiveness
Jordan et al. (2007)	Deer reduction	North America (New Jersey)	Age: General population % Female: NR	NA (surveillance data)	Controlled	Deer removal in treatment towns vs no treatment control towns	Delivery: NA Follow-up: study period 2002-2005	Incidence of Lyme disease Tick density
Malouin et al. (2003)	Education	North America (Baltimore County)	Age: Adults (18 to 65 years) % Female: Intervention 64.2%, Control 65.7%	317	RCT	Postal tick-related education vs general health-materials	Delivery: Mail Follow-up: Pre intervention (spring 1999); follow-up 1 (June/July 1999); follow-up 2 (September/October 1999)	Knowledge, Behaviour Incidence of Lyme disease
Nolan and Mauer (2006)	Education	North America (New York State)	Age: Adults (21 to 63 years) % Female: 26%	190	Controlled	Face-to-face presentation vs mailed information packet	Delivery: Face-to-face or Mail Follow-up: Pre intervention (autumn 1999); post second dose of vaccine (spring 2000, T1)	Knowledge

							and post third dose of vaccine (spring 2001, T2)	
Shadick et al. (2016)	Education	North America (Essex County, MA)	Age: Children (Grades 2 to 5) % Female: 51.1%	3,570	RCT	Classroom education programme vs waitlist control	Delivery: Face-to-face Follow-up: One year	Knowledge, behavioural beliefs, Behaviour, Incidence of Lyme disease
Vazquez et al. (2008)	Protective behaviours	North America (Connecticut)	Age: General population (15 to 70 years) %Female: Intervention 53%, Control 63%	1,191	Retrospective case control	Protection behaviour (various)	Delivery: NA Follow-up: Interviews conducted within a year of diagnosis, recalling a year before diagnosis	Incidence of Lyme disease
Wressnigg et al. (2013)	Vaccination	Europe (Austria and Germany)	Age: Adults (18 to 70 years) % Female: G30a 58%, G60a 55%, G90a 50%, G30n 52%, G60n 59%, G90n 46% ²⁶	300	RCT	Multivalent vaccine administered with or without adjuvant and varied doses: 30, 60 or 90 micrograms	Delivery: NA Follow-up: Three doses primary immunisation, with a booster at 9 to 12 months. The last follow-up was at 10 to 13 months (one month after the final booster)	Vaccine effectiveness and safety

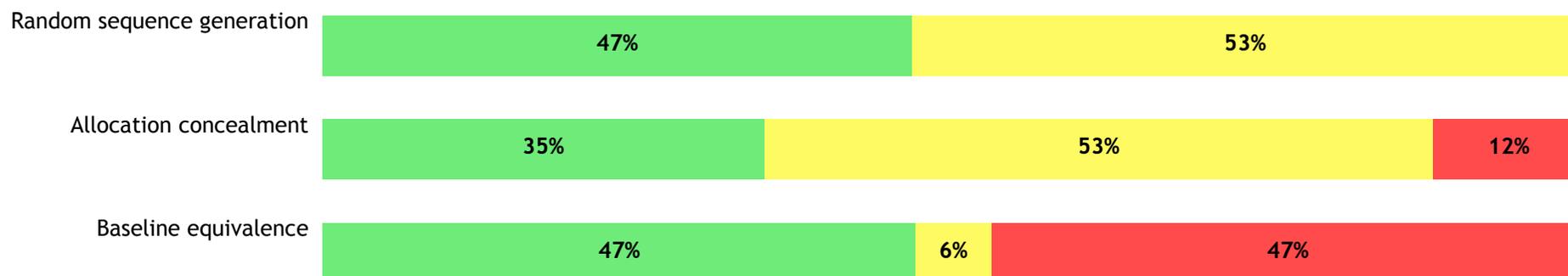
²⁶ G30a = Group 30 microgram dose, adjuvanted, G60a = 60 dose, adjuvanted, G90a = 90 dose, adjuvanted, G30n = 30 dose, non-adjuvanted, G60n = 60 dose, non-adjuvanted, G90n = 90 dose, non-adjuvanted vaccine

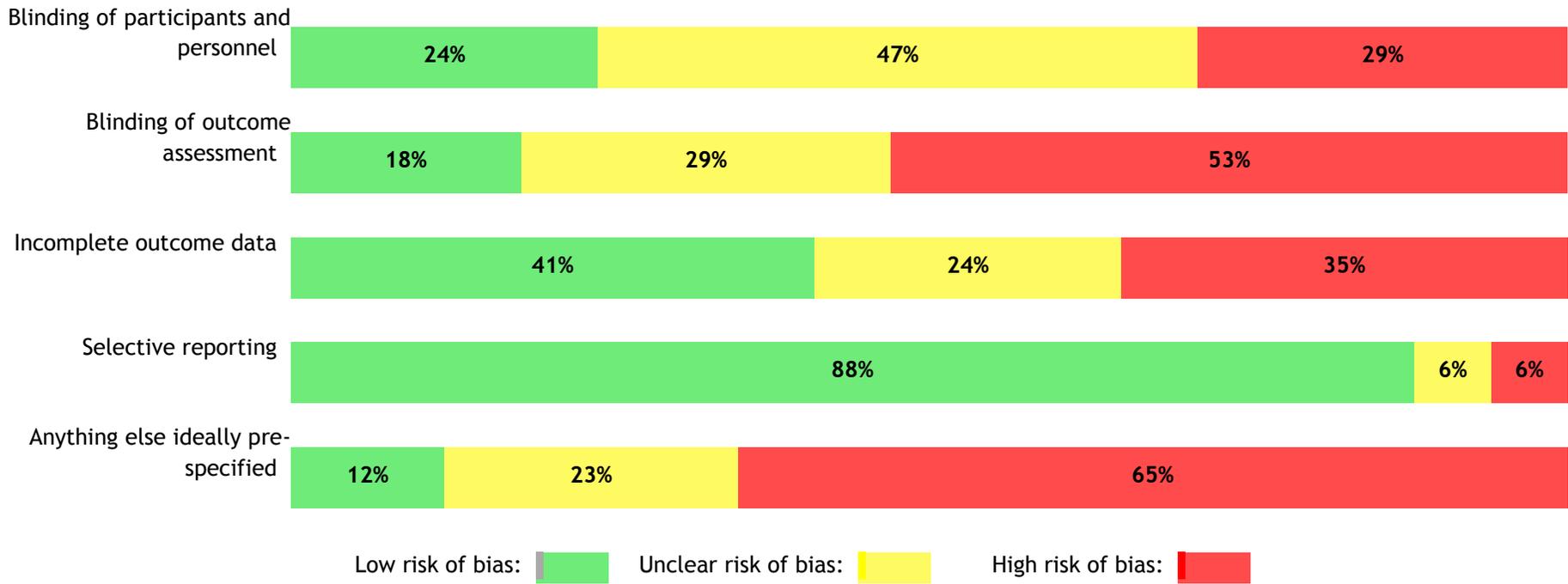
Wressnigg et al. (2014)	Vaccination	Europe (Austria and Germany)	Age: Adults (18 to 70 years) % Female: G30-ve 52.5%, G60-ve 45.9%, G30+ve 45.3%, G60+Ve 32.9%	350	RCT	Multivalent vaccine with adjuvant administered among seropositive or seronegative with varied doses: 30 or 60 micrograms	Delivery: NA Follow-up: Interviews conducted within a year of diagnosis, recalling a year before diagnosis	Vaccine effectiveness and safety
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Appendix 4: Quality appraisal for included studies

Author	Study design	Random sequence generation	Allocation concealment	Baseline equivalence	Blinding participants/personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other (Reliability/validity of measures)	Overall risk of bias
Beaujean et al. (2016a)	RCT	+	?	+	?	-	-	-	-	High
Beaujean et al. (2016b)	RCT	+	?	-	?	-	-	+	+	High
Brewer et al. (2007)	Controlled	?	+	+	-	-	+	+	-	High
Connally et al. (2009)	Case controlled	?	-	-	-	-	-	+	-	High
Daltroy et al. (2007)	RCT	+	?	+	?	+	?	+	+	High
Faulde et al. (2015)	Controlled	?	-	?	-	-	?	+	?	High
Gardulf et al. (2004)	RCT	?	?	-	-	-	+	+	-	High
Garnett et al. (2011)	Controlled	?	+	-	+	?	-	+	-	High
Geier and Geier (2002)	RCT	?	+	-	?	?	?	+	?	High
Hinckley et al. (2016)	RCT	+	?	+	?	?	+	+	-	High

Jordan et al. (2007)	Controlled	?	+	-	+	?	?	?	-	High
Malouin et al. (2003)	RCT	+	?	+	?	-	+	+	-	High
Nolan and Mauer (2006)	controlled	?	?	-	?	-	-	+	-	High
Shadick et al. (2016)	RCT	+	?	+	?	?	+	+	-	High
Vazquez et al. (2008)	Case control	?	?	-	-	-	+	+	-	High
Wressnigg et al. (2013)	RCT	+	+	+	+	+	-	+	?	High
Wressnigg et al. (2014)	RCT	+	+	+	+	+	+	+	?	Low





Appendix 5: Checklist for economic evaluation

Checklist: economic evaluations Study identification Hsia et al. (2002)		
Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5)	Yes/partly/no/unclear/NA	Comments
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Partly	Comparison with no vaccine, other preventative interventions (such as environmental interventions to reduce tick density, education and promotion of precautionary behaviours not considered)
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Pay for health care in USA, incidence rates of Lyme disease may vary.
1.4 Are the perspectives clearly stated and are they appropriate for the review question?	Yes	The number of cases averted is the effectiveness measure more relevant to policymakers, clinicians, and patients; Measuring QALYs requires the determination of utilities for various health states of Lyme disease complications that have not been studied sufficiently.
1.5 Are all direct effects on individuals included, and are all other effects included where they are material?	No	Indirect effects not modelled. Serious adverse effects and problem of misdiagnosis and inappropriate treatment not modelled.
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Costs of long-term sequelae discounted at a rate of 3% per year. The primary outcome measure was the incremental cost-effectiveness (difference in time-discounted direct costs divided by the difference in time-discounted cases of Lyme disease between the vaccine and no-vaccine strategies)
1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above).	No	Cases averted used
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	No	
1.9 Overall judgement: Directly applicable/partially applicable/not applicable	Not applicable	
Other comments:		

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The Department of Health Reviews Facility collaboration has grown out of a previous 'reviews facility' in Health Promotion and Public Health based at the EPPI-Centre, and has been funded by the Department since 1995.

The views expressed in this work are those of the authors and do not necessarily reflect the views of the collaborating centres or the funder. All errors and omissions remain those of the authors.

First produced in 2017 by:

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ISBN: 978-1-911605-02-7

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