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Review Article

Interventions to prevent Lyme disease in humans: A systematic review

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ABSTRACT

Lyme disease (LD) is an infection transferred to humans through bites from infected ticks. Surveillance indicates that the number of LD cases is increasing in the UK, therefore, improved knowledge about reducing transmission from ticks to humans is needed. Eighteen electronic databases were searched and additional web-based searching was conducted, to locate empirical research, published from 2002 onwards. Sixteen studies that evaluated five types of prevention intervention were included: personal protection (n = 4), domestic strategies (landscape modification and chemical pest control) (n = 3), education (n = 6), vaccination (n = 3), and deer-reduction programmes (n = 2). In general the quality of evidence was low. Results suggest that personal protection strategies, including the use of tick repellents and wearing of protective clothes, can prevent tick bites and reduce the incidence of LD among adults. Educational interventions were generally successful for improving adults' knowledge, behavioural beliefs (e.g., self-efficacy for performing tick checks) and preventative behaviour, but for children, the findings were mixed. For adults and children, knowledge changes did not typically translate into a lower incidence of LD. Whilst evidence on vaccination against LD is promising, too few studies were available to reach robust conclusions. There was no evidence of effectiveness for deer culling, and the evidence was inconclusive for applying acaricide (tick poison) to deer's ears and heads. Low-quality evidence suggests 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, vaccination and deer programmes is needed.

1. Introduction

1.1. Lyme disease (LD)

LD is caused by the *Borrelia burgdorferi* sensu *lato* bacterium that can be spread to humans by infected ticks. Surveillance suggests that the number of cases of LD is increasing in Europe and North America (Lorenc et al., 2017). A common early sign of the disease is an erythema migrans or a ‘bulls-eye’ rash surrounding the bite (Wormser et al., 2006). Some people also report flu-like symptoms (fatigue, muscle pain, headaches, fever and neck stiffness) (NHS, 2018). More serious and persistent symptoms (chronic LD) may develop if not treated or after treatment (post-treatment LD), including pain and swelling in the joints, problems affecting the nervous system, and heart problems (NHS, 2018). However, there is controversy over the existence of persistent symptoms and there is no agreed treatment (Rebman et al., 2017 p.535).

1.2. Previous research on prevention interventions for LD

Prevention is preferable to treating the consequences of tick-borne diseases, therefore, understanding which strategies are effective in preventing transmission to humans is beneficial. Four systematic reviews on LD prevention were located in our evidence map on LD in humans (Stokes et al., 2017),[1] discussed, below.

Mowbray et al. (2012) suggested a number of effective educational interventions to encourage protective behaviours against tick-borne disease. These included postal information, educational ‘shows’ and

Abbreviations: CI, confidence interval; DEET, *N*,*N*-diethyl-meta-toluamide (an insect repellent); NHS, National Health Service; GP, general practitioner; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk; SE, standard error; SS, statistically significant; TBI, tick-borne infections

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[1] The findings of a systematic evidence map covering the whole range of research evidence on Lyme disease in humans (Stokes et al., 2017) were used to populate a number of focused, systematic evidence reviews, including this review on prevention methods.

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videos, one-to-one education with a physician, public campaigns, and interactive programmes for children. However, of the nine studies reviewed, over half adopted a non-controlled design, therefore, there is some uncertainty about the robustness of their conclusions.

Two recent systematic reviews focused on LD vaccines that are no longer available on the market. Zhao et al. (2017) concluded that whilst side-effects were rare, further research on efficacy and safety was needed. Badawi et al. (2017) compared monovalent vaccines (LYMErix, ImmuLyme) (neither currently available) with preliminary data for next-generation multivalent vaccines and concluded that the multivalent vaccine was slightly more tolerable than the monovalent one, which in turn was not worse than other vaccines in the USA-based Vaccine Adverse Event Reporting System (VAERS). Despite approval for the LYMErix vaccine by the US Food and Drug Administration (FDA), the LYMErix vaccine was voluntarily withdrawn from the market, in 2002, due to poor sales. The replacement of monovalent vaccines with vaccines that have a similar approach may, therefore, not be the best method for new vaccine development (Badawi et al., 2017).

Only one review examined the effect of antibiotic prophylaxis (after a bite). In this review, Warshafsky et al. (2010) concluded that pooled data from four placebo-controlled trials supported the use of antibiotic prophylaxis in endemic areas.

Existing reviews on the prevention of LD in humans have each focused on a single strategy, such as education, vaccination or antibiotic prophylaxis. We found no systematic reviews on personal protection (such as wearing protective clothing or insect repellent) or domestic protection (such as landscape modifications and chemicals to reduce tick populations in the garden), or deer interventions (the primary host of ticks).

This review aims to bring together the evidence on all prevention strategies to establish which interventions that aim to prevent LD in humans are effective.

2. Methods

2.1. Study identification

This review was prospectively registered with PROSPERO.[2] Methods were in accordance with the guidelines of the University of York's Centre for Reviews and Dissemination, and Cochrane. Included studies were initially identified for a systematic evidence map, covering a wide range of research evidence on LD (Stokes et al., 2017). Details of the databases searched and an example search strategy are provided Appendix A. Bibliographic database searches were conducted in August 2016. For full details of the methods and findings of the systematic map, see Stokes et al., 2017.

2.2. Inclusion criteria

To be included in the review studies needed to:

- Be published in or after 2002[3]
- Be published in the English Language
- Evaluate the effectiveness of interventions which aimed to reduce the incidence of Lyme disease in humans (i.e., prevention studies)
- Include a control (of any type)
- Include efficacy outcomes. For vaccination studies, immunogenicity (strength of immune response) and safety outcomes, measured in phase 1 and 2 trials, were included

All studies considered for inclusion in the systematic review were screened independently by two reviewers using the full text. All disagreements were resolved by discussion between these researchers.

[2] CRD4201707151.

[3] As advised by our scientific advisory group, to reflect current experiences and practices relating to LD.

2.3. Data extraction

A data-extraction form was developed and piloted to record the relevant study and participant characteristics, outcomes and quality assessment. Outcomes assessed included knowledge, behavioural beliefs, behaviour, incidence of tick bites and/or LD and the immunogenicity and safety of vaccinations.

Included studies were rated for quality using a modified Cochrane Risk of Bias tool (Higgins et al., 2011) that incorporated elements of the ROBINS-I tool for non-randomised designs (see Sterne et al., 2016). This tool was initially applied by two reviewers independently until it could be applied with a 90% agreement rate.

2.4. Synthesis

Data were synthesised narratively by intervention, study design and outcome type.

Between-group effect size estimates for the study outcomes are reported (where available), in terms of whether or not the direction of the effect supports the prevention strategy and if the effect was statistically significant.

3. Findings: What types of interventions are effective in preventing LD?

3.1. Overview of included studies

Of 82 full texts screened, sixteen met our inclusion criteria.[4] Searching the reference lists of four systematic reviews did not lead to any further eligible studies. The flow of literature through the review, is reported in Appendix B.

Five types of intervention were identified: personal protection (n = 4), domestic strategies (n = 3), education (n = 6), vaccination (n = 3), and deer-targeted programmes (n = 2).[5] None of the antibiotic prophylaxis interventions, screened at full text, met our criterion of published in 2002 or later.

Included evaluations were conducted in the USA (n = 10), or Europe[6] (n = 6). Study designs included randomised controlled trials (RCTs) (n = 9),[7] matched case-control studies (n = 3), and observational controlled studies (n = 4). Seven studies each, targeted the general population and adults only[8]; two targeted children. All studies, but one, were rated as 'low-quality' (mainly due to inadequate blinding of participants and personnel and reliance on self-reported outcome measures). Characteristics of the included studies and their quality assessments are provided in the appendices (C and D). (See Boxes 1–5.)

3.2. Personal protection (n = 4 studies)

3.2.1. Personal protection for preventing LD

Two matched case-control studies sampled participants with and without LD (Connally et al., 2009; Vazquez et al., 2008). Findings showed that the use of tick repellents on skin or clothing was associated with lower rates of LD (adjusted[9] OR 0.8, 95% CI 0.6 to 0.9 for Vazquez

[4] A list of papers excluded at full-text stage is available from the lead author. Vaccine studies that did not included efficacy outcomes were excluded from these analyses.

[5] Two studies reported both personal and domestic prevention interventions.

[6] Austria, Germany, Sweden, and the Netherlands.

[7] One of which (Shadick et al., 2016) was cluster randomised (by district).

[8] One targeted a Military population (assumed to be adults).

[9] After adjusting for potential confounders (gender, race, receipt of Lyme vaccine, and the use of other personal protective measures).

Box 1
Summary of findings.

Low-quality evidence suggests that:

- Tick repellents and protective clothing may be associated with a lower incidence of LD (n = 2).
- Effects were mixed for the association between tick checks and incidence of LD (n = 2).
- Bathing within 2 h of being outside may be associated with a lower incidence of LD (n = 1).
- Permethrin-treated battle dress uniform (n = 1) and Citriodiol insect repellent (n = 1) may reduce the number of ticks crawling or bites.

Note: The summary refers to the direction of effect only; for details of effect size, confidence intervals and statistical significance, refer to the text.

Box 2
Summary of findings.

Low-quality evidence suggests that:

- Having a fence or stone wall, trimming overhanging branches, having a dry barrier, spraying the yard, and killing other pests may be associated with a lower incidence of LD (n = 1).
- Mowing the lawn frequently, and having a vegetable garden, bird feeder, woods near the property, log pile and clearing leaves may be associated with a higher incidence of LD (n = 1).
- Spraying properties reduces the frequency of ticks crawling or attached (n = 1).
- Effects were mixed for spraying property on the incidence of LD (n = 3).

Note: The summary refers to the direction of effect only; for details of effect size, confidence intervals and statistical significance, refer to the text.

Box 3
Summary of findings.

Low-quality evidence suggests that:

- Education (leaflet or video, mail, presentation and live show) may increase adults' general knowledge, efficacy and behavioural intention of taking preventive measures (n = 3).
- Education (postal information) may increase protection behaviour (including the use of repellent containing DEET, permethrin on clothing, and tick checking) (n = 1).
- Education (live show) may reduce the incidence of LD (n = 1).
- Classroom education may increase children's knowledge, self-efficacy for tick checking, tick checking frequency, and the wearing of long pants (n = 1).
- Education (game and leaflet) may be ineffective in promoting children's knowledge about LD and tick check frequency (n = 1).

Note: The summary refers to the direction of effect only; for details of effect size, confidence intervals and statistical significance, refer to the text.

Box 4
Summary of findings.

Low- and high-quality evidence suggests that:

- Multivalent vaccine may produce an immune response that helps to prevent LD and is well tolerated (n = 2).

Low-quality evidence suggests:

- Reduced use of preventative behaviour (e.g., use of tick repellent) with LYMErix vaccine (n = 1).

Note: The summary refers to the direction of effect only; for details of effect size, confidence intervals and statistical significance, refer to the text.

Box 5
Summary of findings.

Low-quality evidence suggests that:

- Deer removal may reduce tick abundance compared with control (n = 1).
- Effects were mixed for the impact of deer removal on the incidence of LD (n = 1).
- Effects were mixed for the impact of acaricide, applied to deer's ears and heads, on the incidence of LD (n = 1).

Note: The summary refers to the direction of effect only; for details of effect size, confidence intervals and statistical significance, refer to the text.

et al., 2008; OR 0.71, 95% CI 0.49 to 1.02, $p < 0.1$ for Connally et al. (2009). Similarly, Vazquez et al. (2008) showed that wearing protective clothes was effective (adjusted OR 0.6, 95% CI 0.5 to 0.7). Connally et al. (2009) ($p > 0.20$) reported that wearing light-coloured clothes (cases 88% v controls 90%) and long trousers (cases 65% v controls 70%) were less common among people diagnosed with LD, compared with controls, but the differences were not statistically significant.

The evidence was mixed for tick checking; being identified as preventative in Connally et al. (2009) (OR 0.64, 95% CI 0.43 to 0.94), but not in Vazquez et al. (2008) (OR 1.1, 95% CI 0.8 to 1.4, NS). Connally et al. (2009) additionally showed that bathing within 2 h of being outside in the garden may prevent LD (OR 0.60, 95% CI 0.38 to 0.96, $p < 0.05$).

3.2.2. Personal protection for reducing tick-bites

Low-quality evidence suggested that permethrin-treated (vs. untreated) battle uniform (Faulde et al., 2015) and Citriodiol insect repellent (Gardulf et al., 2004) may reduce the frequency of tick bites. Faulde et al. (2015)'s historical controlled study showed that in 2009, tick bite incidence was 39.3 with 262 bites in 66,679 exposure days, whilst in 2010 (when the treated uniform was worn) the incidence was 0.16 with 53 bites in 63,571 exposure days (representing a 99.6% reduction). The same pattern of findings was reported in 2011 (representing a 98.6% reduction).

In Gardulf et al. (2004)'s crossover RCT, lemon eucalyptus extract (Citriodiol[10]) was self-applied to participants' legs. Overall, there were fewer tick bites per person with the spray compared with no spray, (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).

3.3. Domestic strategies (n = 3 studies)

3.3.1. Domestic strategies for preventing LD

One case-control study, (Connally et al., 2009) indicated that 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, albeit not significant statistically. In terms of risk factors for LD, the following landscape features were identified (contrary to advice): having a log pile (cases 53% v controls 50%, $p > 0.2$), clearing leaf litter (cases 54% v controls 46%, $p > 0.2$), 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). Consistent with advice, having a birdfeeder (OR 1.29, 95% CI 0.89 to 1.98) and having woods near the property (OR 1.32, 95% CI 0.89 to 1.98) were also risk factors for LD.

Three studies evaluated chemical solutions; two case-control studies (Connally et al., 2009; Vazquez et al., 2008) and one RCT (Hinckley et al., 2016).

In both case-control studies, spraying acaricide was protective against LD, although the effects were small and not statistically significant (cases 10% v controls 12%, $p > 0.2$ in Connally et al. (2009); OR 0.6, 95% CI 0.3 to 1.1 in Vazquez et al. (2008)).

3.3.2. Domestic strategies for reducing tick contact

Using a RCT, Hinckley et al. (2016), reported that the incidences of ticks found crawling on a person or attached were 24.9% and 16.3%, respectively, in households with chemical treatment (vs. those without 27.9%, $p = 0.08$ and 17.8% $p = 0.33$, NS, respectively). However, for illness five to six months after intervention, there was no significant difference between households when self-reported (sprayed, 3.2%; without, 3.0%; $p = 0.78$) or verified using medical records (1.5% sprayed, 1.6% without $p = 0.90$).

3.4. Education (n = 6 studies)

All but one non-randomised controlled study (Nolan and Mauer, 2006) employed a RCT design. Due to the high number of knowledge outcomes, for clarity and accessibility of text, the effect sizes and p-values are tabularised in the Appendix (E).

3.4.1. Education for general knowledge, self-efficacy, behavioural intention, protection behaviour and incidence of LD among adults

Overall, for adults, education interventions (leaflet or video, postal information, presentation and live show) were generally found to be successful for improving knowledge (Beaujean et al., 2016a; Daltroy et al., 2007; Malouin et al., 2003; Nolan and Mauer, 2006). Furthermore, in Beaujean et al. (2016a), behavioural beliefs (including self-efficacy for recognising and managing a tick bite, belief that preventative behaviour will help,[11] and intention to engage in protective behaviour) were higher, adjusting for potential confounding variables, in the leaflet and movie groups, compared with the control, immediately post intervention. However, at four-week follow-up, whilst the effects remained in the same direction, they did not retain statistical significance. These positive effects for behavioural beliefs, however, did not translate into preventative behaviour (e.g., tick checking and visiting a GP) (effect size estimates and statistical tests were not reported).

By contrast, participants in Malouin et al. (2003)'s tick-related education programme were more likely to have used repellent containing DEET, to have used acaricide containing permethrin on clothing, to have checked for tick bites and to have checked more thoroughly (using a mirror), compared with control. However, tick checks away from home only supported the intervention at three-month follow-up (NS). Contrary to expectation, self-reported tick bites were more common in the postal educational intervention than the control (NS). A threefold increase in a potential tick-bite bio-marker was observed among three control participants, compared with two

[10] Citriodiol is available, in the UK, in insect repellents, such as Mosi-guard Natural.

[11] Statistically significant in leaflet condition only.

participants in the intervention group.

Nolan and Mauer (2006)'s study found that a face-to-face educational session was more effective than a mailed information packet among adult participants deciding whether to receive a vaccine for LD.

In Daltroy et al. (2007), ferry passengers (traveling to an endemic area for LD) randomised to an educational programme on LD and other tick-borne infections (TBI) were more likely to take precautions (use repellent, protective clothing, and limit time in tick areas; pooled) than controls receiving bicycle safety education. Self-reported rates of TBI, after two months, were lower among intervention participants than controls (NS). However, controlling for covariates,[12] there were statistically significant reduced rates of TBI among the intervention participants (1.58) vs. controls (3.71), when staying for longer than two weeks (RR 0.41, 95% CI 0.18 to 0.95, $p < 0.038$).

3.4.2. Education for general knowledge, self-efficacy, behavioural intention, protection behaviours and LD incidence among children

Shadick et al. (2016) showed that a short in-class education programme impacted positively on children's knowledge about LD, self-efficacy in checking /finding a tick on self, and wearing long trousers, compared with the waitlist control. Of 72 parents contacted, only five reported LD infection (two were confirmed by GP records).

By contrast, Beaujean et al. (2016b) showed that the control had greater knowledge about LD, compared with the video and the leaflet conditions (albeit NS).

3.5. Vaccination (n = 3 studies)

3.5.1. Vaccination for preventing LD

Two RCTs (Wressnigg et al., 2014; Wressnigg et al., 2013) assessed the immunogenicity of a new multivalent vaccine for preventing LD. Wressnigg et al. (2013) found that whilst all doses (30, 60 or 90 µg), given on three occasions 28 days apart, and formulations (with or without an adjuvant to enhance the effect[13]) produced a positive response, the 90 µg non-adjuvanted formulation produced the highest response after the first three vaccinations. However, after a booster (9 to 12 months later), the 30 µg adjuvanted dose was most effective.

Wressnigg et al. (2014) compared healthy people who were either seropositive[14] or seronegative[15] for LD. Participants received three doses (30 or 60 µg of vaccine with aluminium hydroxide adjuvant) 28 days apart, with a booster at 6 months or 9 to 12 months. In seronegative people, the antibody responses induced by the dose formulations were similar ($p = 0.062$; range for 30 µg, 3799 to 6937, for 60 µg, 4575 to 8543). In seropositive people, the 60 µg dose (range, 4895 to 9435) resulted in significantly higher antibody response than the 30 µg dose (range, 2413 to 4371; $p = 0.0001$). The booster response was effective at both time points, but more so when administered at 9 to 12 months. However, there was a dose effect among seropositive participants favouring the higher (60 µg) dose ($p = 0.0359$; for five[16] of the six serotypes, (range 28,735 to 42,381), over the 30 µg dose (range 12,653 to 17,485).[17]

3.5.2. Vaccinations and adverse events

Two studies assessed the newer multivalent vaccine (Wressnigg et al., 2014; Wressnigg et al., 2013). Wressnigg et al. (2013) reported lower reactions in the adjuvanted group, compared with non-adjuvanted formulations (systemic reaction RR = 0.54, 95% CI 0.41 to 0.70; $p < 0.0001$ and for moderate or severe systemic reactions RR = 0.35, 95% CI 0.13 to 0.92; $p = 0.034$). The 30 µg adjuvanted formulation had the best tolerability profile, although both studies were small.

Wressnigg et al. (2014) also assessed injection site events (e.g., swelling) and systemic events (e.g., headache or fatigue) within seven days of injection. There were no statistical differences between seronegative and 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). No serious vaccine-related adverse events were reported, and there were no symptoms of Lyme borreliosis or chronic arthritis. On the basis of the adverse events and antibody titres, the authors identified the 30 µg adjuvanted dose as the best formulation.

3.5.3. Vaccinations and changes in risk behaviour

One study (Brewer et al., 2007) assessed the impact of LYMErix on changes in risk perception and prevention behaviour for LD in adults.

Interactions between groups (vaccinated vs not vaccinated) by time (baseline and 18 months later) indicated that the use of tick repellent ($p < 0.10$) and wearing of light clothes ($p < 0.05$), were reduced more among those who received the vaccine than those without. Nonetheless, their prevention behaviour remained above that of the non-vaccinated group (means not reported).

3.6. Deer programmes (n = 2 studies)

3.6.1. Deer programmes for reducing tick abundance and incidence of LD

Two studies examined the effects of deer programmes (Garnett et al., 2011; Jordan et al., 2007), using a before-and-after, treatment-control design that involved culling the primary host of the black-legged tick that carries LD.

In Jordan et al. (2007), mean tick abundance for the study years (2002 to 2005) was statistically less, compared with the control sites, across life-stage of the tick: spring adults[18] (cull mean ± SE: 1.2 ± 0.2; control mean ± SE: 4.9 ± 0.8, $F = 16.92$, $p < 0.01$), nymphs (cull mean ± SE: 1.5 ± 0.2, control mean ± SE: 2.5 ± 0.2, $F = 13.89$, $p < 0.01$), larvae (cull mean ± SE: 6.7 ± 0.7, control mean ± SE: 37.7 ± 6.0, $F = 16.22$, $p < 0.01$) and fall (autumn) adults (cull mean ± SE: 1.5 ± 0.2, control mean ± SE: 6.5 ± 0.9, $F = 28.18$, $p < 0.01$). Nonetheless, overall, there was no decrease in the abundance of ticks due to the removal of deer.

In Garnett et al. (2011), the difference in relative rate of incidence of LD in culling areas, compared with control areas, before (relative rate = 13.04), and after (relative rate = 6.99) treatment, did not obtain statistical significance (Mann-Whitney U = 30.5, $p = 0.244$).

Garnett et al. (2011) additionally examined a treatment device that applied acaricide to deer's ears and heads.[19] The difference in relative rate of incidence of LD that compared original treatment with control areas before (relative rate = 3.93), and after (relative rate = 2.38) treatment, was statistically significant in the expected direction (Mann-Whitney = 74.0, $p = 0.040$). For both the cull and acaricide interventions, the pattern of effects was replicated with the expanded control

[12] 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.

[13] 1 mg aluminium hydroxide per dose, used to enhance the effects of the vaccine, but not provide immunity alone.

[14] Meaning that their blood tested positive, although they displayed no symptoms.

[15] Their blood tested negative for antibodies.

[16] Unclear which one was not different, possibly serotype 1.

[17] 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.

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

[19] Acaricide applied to deer's ears and heads.

group.[20]

4. Discussion

This review examined the effectiveness of a range of strategies to prevent LD. Personal protection was the most effective strategy with consistent (albeit) low-quality evidence for the use of tick repellents and wearing protective clothes among adults. Educational interventions, targeted at adults, were generally successful for improving knowledge and behavioural beliefs (e.g., self-efficacy for performing tick checks) whereas, among children, the evidence was mixed. However, for both adults and children there was little evidence that change in beliefs and behaviour led to a reduction in tick bites and LD. The evidence on vaccination against LD is promising, but the few studies available were too small to reach robust conclusions about effectiveness and safety. For culling deer, there was no evidence of effectiveness, and for applying acaricide to deer's ears and heads, the evidence was inconclusive.

4.1. How do these findings compare with previous research?

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 the full range of approaches to prevention has been collectively reviewed systematically.

Consistent with Mowbray et al. (2012), the findings indicate that educational material could be effective among adults. Nonetheless, it is still unknown which educational methods, if any, could modify behaviour in such a way that the rate of tick-borne illness is reduced. The evidence from two child-based intervention studies, published since Mowbray et al. (2012), was mixed.

A range of educational methods was examined (including leaflet, video, game, postal information, in-class face-to-face sessions, and live entertainment on a ferry) that 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), and social interaction (Shadick et al., 2016). This brings into question which of the elements was responsible for modifying changes in perception and behaviour, where it occurred.

The findings on vaccination are consistent with Zhao et al. (2017), suggesting that the newer multivalent vaccines produce an immune response. Nonetheless, due to short follow-up periods, and small sample sizes, consistent with Zhao et al. (2017), it is concluded that more robust evidence is needed to examine potential adverse effects and to guide the development and testing of a marketable vaccine to prevent LD in humans.

Current European and USA prevention guidance for LD relates mostly to personal behaviour that aims to prevent tick bites occurring (such as the use of tick repellents, wearing of protective clothes, avoiding infested regions and tick checking) and is, therefore, consistent with the findings of this review (WHO, 2018).

4.2. Strengths and limitations

The broad focus helped to ensure a comprehensive synthesis of available research. Nonetheless, the inclusion of only the previous 15 years of research may have led to potentially useful studies being excluded from the review. Because of the range of interventions and the heterogeneity of methods, the planned meta-analysis was not conducted. Consequently, sampling and measurement errors could not be accounted for. Furthermore, 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. Given the range of outcomes and measures, it was not possible to present standardised information about the size of effects across the studies. Objective measures of the incidence of LD (i.e., GP records of diagnoses), that correspond to the local tick season and employ long follow-up periods, are needed to reliably assess effectiveness. Thus, more high-quality research is needed for reliable conclusions to be reached.

Studies examining the effectiveness of personal protection and education methods in different country settings, especially Europe, are warranted. Qualitative exploration of the different strategies would be a useful addition, particularly in understanding the barriers and enablers of preventative behaviour. Similarly, more trials to assess the efficacy and safety of vaccination to prevent LD and deer-targeted programmes are warranted; for vaccination studies, as most were funded by drug companies, more independent research is needed. Measures of risk perception could usefully be included in vaccination studies, and demographics (such as social economic status and ethnicity) could be assessed more generally, as few studies reported these. Due to the lack of recent research on antibiotic prophylaxis and checking pets for ticks, more work in these preventative areas would be beneficial.

Overall, these findings provide support for personal protection (especially tick repellent and wearing protective clothes). These prevention behaviours can be successfully encouraged, among adults, using education interventions, although education was not generally associated with a reduction in tick bites or incidence of LD. Whilst the evidence for vaccination against LD is promising, as is evidence for the topical application of acaricide to deer's ears and heads, further research is needed to examine the effectiveness of these interventions.

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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 EPPI-Centre, the Centre for Reviews and Dissemination or the funders. Responsibility for the views expressed remains solely with the authors.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2018.11.004.

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[20] 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 sixth year of treatment, however, no between-group comparisons were reported.

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