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Environmental Evidence

SYSTEMATIC REVIEW PROTOCOL

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Can interventions that aim to decrease Lyme disease hazard at non-domestic sites be effective without negatively affecting ecosystem health? A systematic review protocol

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Abstract

Background: Lyme disease (LD) is the most commonly reported, broadly distributed vector-borne disease of the northern temperate zone. It is transmitted by ticks and, if untreated, can cause skin, cardiac, nervous system and musculoskeletal disease. The distribution and incidence of LD is increasing across much of North America and Western Europe. Interventions to decrease exposure to LD hazard by encouraging behavioural change have low acceptance in high risk groups, and a safe, effective human LD vaccine is not presently available. As a result, habitat level interventions to decrease LD hazard itself (i.e. levels of infected ticks) have been proposed. However, some interventions may potentially negatively affect ecosystem health, and consequentially be neither desirable, nor politically feasible. This systematic review will catalogue interventions that aim to reduce LD hazard at non-domestic sites, and examine the evidence supporting those which are unlikely to negatively affect ecosystem health.

Methods: The review will be carried out in two steps. First, a screening and cataloguing stage will be conducted to identify and characterise interventions to decrease LD hazard at non-domestic sites. Secondly, the subset of interventions identified during cataloguing as unlikely to negatively affect ecosystem health will be investigated. In the screening and cataloguing step literature will be collected through database searching using pre-chosen search strings, hand-searching key journals and reviewing the websites of public health bodies. Further references will be identified by contacting stakeholders and researchers. Article screening and assessment of the likely effects of interventions on ecosystem health will be carried out independently by two reviewers. A third reviewer will be consulted if disagreements arise. The cataloguing step results will be presented in tables. Study quality will then be assessed independently by two reviewers, using adapted versions of established tools developed in healthcare research. These results will be presented in a narrative synthesis alongside tables. Though a full meta-analysis is not expected to be possible, if sub-groups of studies are sufficiently similar to compare, a partial meta-analysis will be carried out.

Keywords: Borreliosis, Evidence synthesis, Control measures, One health, Vector-borne, Ticks, *Ixodes*, Medical acarology, Integrated pest management, Zoonoses

Background

Transmitted by blood-feeding ticks, Lyme disease (LD) is the most common vector-borne disease of the temperate northern hemisphere and is caused by a bacterial infection of *Borrelia burgdorferi* s.l. (*Bb*) [1]. Initial symptoms of LD can be relatively mild, and the early prescription of antibiotics is effective at reducing its severity [2]. However, if untreated, LD can progress to serious systemic disease, involving skin, cardiac, nervous system, and musculoskeletal damage [3]. Though physician records resembling LD date back to the nineteenth century, it

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was not until the 1970s that LD per se was described and *Ixodes* ticks identified as vectors [4].

Annual incidence is estimated at 106.6 per 100,000 persons in the USA [5], with the great majority of cases arising in northeastern and northern midwestern states [4]. Similarly whilst incidence across Western Europe is estimated at 56.03 per 100,000 people, it differs significantly between countries, ranging from 0.001 per 100,000 (Italy) to 464 per 100,000 (Sweden) [6]. In Europe, as in the USA [7, 8], the geographic spread and reported number of clinical cases is rising in many areas [9–11]. In some countries the increase in reported cases may partly be explained by growing awareness amongst clinicians and the public about disease symptoms and transmission routes [12]. However, there is also strong evidence ecological and social determinants are driving increased incidence. Ecological factors that have been associated with rising LD hazard include reafforestation, habitat fragmentation, changes in vector distribution and abundance, and shifts in the community composition and population dynamics of predators and tick hosts [13]. Disease risk is further shaped by social practices which can increase human exposure to LD hazard, such as outdoor recreational pursuits, and the construction of housing within forest matrices [13]. The relative contribution of many of these factors to LD emergence remains contested, but is likely to differ between and within countries [14], partly explaining the geographical disparity in incidence rates and patterns of disease risk across the northern temperate zone. Reported cases are likely to be an underestimate of actual LD prevalence. For example, tests of Scottish blood donor supplies found 4.2 % (60/1440) were seropositive for *Bb* whilst the Scottish (laboratory confirmed) incidence rate is reported at 9.82 cases per 100,000 persons [15]. This, alongside similar screening of occupationally high risk groups [16, 17], suggests many people are bitten by *Bb* infected ticks, but either do not develop LD or receive a diagnosis.

Vaccination and encouraging precautionary behaviour change have had only limited success with LD and in some cases faced outright opposition. A human LD vaccine licensed in the USA in 1998 was withdrawn by its producer 3 years later following sales drops amidst a health scare catalysed by anti-vaccine groups [18]. New vaccines in development could have greater commercial viability as they are designed to target multiple *Borrelia* or tick vectors, and thus work across larger geographic areas [19–21]. Nevertheless, they are still likely to face major barriers to widespread adoption [22]. Recommended precautionary behaviours designed to decrease the risk of being bitten by infected ticks include wearing light coloured clothes with long sleeves and trousers tucked into socks, the use of insecticide on skin and clothing, sticking to paths and avoiding walking through long grass [23, 24]. Despite considerable effort to popularise them, many of these measures remain largely un-adopted. One recurring theme in interviews with UK park visitors was resistance to viewing the countryside as a place that included risk, in part because it clashed with framing of visits to such places as restorative. This led some interviewees to oppose on-site signage and leaflets, whilst the common advice to wear long sleeves and trousers was rejected as it would reduce their enjoyment of summer [25]. Even amongst those who had previously suffered LD, during-visit precautionary measures remained unpopular [26]. Similar findings have been reported from the Netherlands [27], the USA [28], Switzerland and Canada [29]. Even when adopted, most personal preventative measures are not highly effective [30–32]. Whilst some innovations promise greater risk reduction, especially those relating to acaracide treated clothes [33], basic social barriers to engagement remain. For instance, in recent work by Mowbray et al. [34] respondents stated they would not follow advice to tuck trousers into socks. A common explanation for why: 'Because I'd look stupid.'

Following a case-controlled evaluation, Vázquez et al. [32] concluded educational work to encourage personal preventative measures should continue, but given its limited success so far and the unavailability of a vaccine, habitat level interventions to decrease LD hazard should be developed in areas of high tick-human contact. Unfortunately, some suggested tactics may negatively affect ecosystem health. For example, acaracide spraying to control LD may potentially impact non-target species [35], as happened across multiple trophic levels with DDT [36], which was sprayed by air over much of the Soviet Union as a control strategy for Tick-borne encephalitis [31]. A reduction of LD hazard may potentially be made possible by eradicating the animals and birds that act either as reservoirs of the *Bb* pathogen, or as hosts supporting tick vector populations through blood-meal provision (for example deer [37]). Eradications may seem justified from a narrow pathogen-focused perspective, but community disassembly may have significant effects on ecosystem function, especially where the disease system involves a diverse range of species. As areas with high tick-human contact are often managed for both recreation and biodiversity such actions may neither be desirable nor politically feasible [29, 38]. More broadly there is active debate within Public Health about the ethics involved in widespread culling of wildlife as a disease control strategy [39]. With such issues in mind, and given the continuing emergence of LD across the northern temperate zone, an evidence synthesis of interventions which are unlikely to negatively affect ecosystem health is much needed.

This systematic review will catalogue interventions to decrease LD hazard at non-domestic sites, and evaluate the evidence supporting those assessed as unlikely to negatively

affect ecosystem health. Such interventions range from those presumed to have a generally neutral effect on ecosystems (acaracide application to wild or domesticated animals, [40, 41] and vaccines for reservoir hosts [42]), to ones which may have win–win outcomes for public health and conservation (local deer exclusion or reduction [43], predator reintroduction [44–46], decreasing forest fragmentation [47], removal of invasive trees as part of habitat restoration [48] and woodland biodiversity management [49]).

Objective of the review

The systematic review's objective is to catalogue interventions to decrease LD hazard at non-domestic sites, and assess the evidence for effectiveness of a subset identified as unlikely to negatively affect ecosystem health. A scoping search found no published or prospectively registered systematic reviews with the same topic. Domestic measures (such as gravel barriers separating garden lawns from woodland ecotones) may reduce hazard where residential exposure is of high concern [50]. However, the focus of this review will be on interventions which could be carried out at non-domestic sites, such as Country Parks, where the greatest number of people exposed to LD hazard are recreational visitors. Such sites differ in size within and between countries, but for illustration UK accredited Country Parks range from a minimum of 10 hectares [51] to over 1000 [52]. In larger Parks, such as National Parks, visitors often concentrate at a small numbers of key locations [53, 54] within this spatial range, where interventions to reduce LD hazard could potentially be incorporated into existing site management plans [55]. The project's target audience is: (a) land managers such as local authorities and conservation organisations; and (b) scientists and public health bodies involved in research around LD and tick-borne diseases.

The screening and cataloguing step will identify interventions and asses their likely effects on ecosystem health. The systematic review will then analyse the subset of interventions identified as unlikely to negatively affect ecosystem health to answer the review's primary research question: which interventions to decrease Lyme disease hazard at non-domestic sites are unlikely to negatively affect ecosystem health and what evidence exists to support their effectiveness?

Components of the primary research question

Population

Non-domestic sites (i.e. lands not adjoining and belonging to a house) with LD hazard (i.e. *Bb* infected ticks of one or more species known to feed on human blood). The geographical scope of the review will be global, but is likely to reflect the predominantly northern hemispheric distribution of *Bb*.

Intervention

Any intervention to reduce site LD hazard, that is assessed as unlikely to negatively affect ecosystem health (as defined in the "Data synthesis and presentation" section).

Comparator

No intervention or an alternative intervention.

Outcomes

Spatial and/or temporal distribution and abundance of site LD hazard. It is expected studies will have quantified this differently.

Methods

The systematic review will be carried out in two steps. First, a screening and cataloguing step will identify and characterise interventions to decrease LD hazard at non-domestic sites. This will include identifying subsets of interventions that, (i) would be unlikely to negatively affect ecosystem health, or (ii) would be likely to negatively affect ecosystem health. Subsequently, the subset of interventions identified as unlikely to negatively affect ecosystem health will be investigated, and their effectiveness at reducing LD hazard determined.

Prospective registration of review

As the review topic bridges public health and environmental management, it is registered with both the Collaboration for Environmental Evidence and PROSPERO, the international database of prospectively registered systematic reviews in health and social care (Unique ID CRD42016046629) [56].

Searches

The flowchart in Fig. 1 illustrates the systematic review pathway. Articles will be collected primarily through database searching with other literature suggested by stakeholders and researchers in the field.

Search terms and languages

Table 1 shows search terms and search strings to be used. Searches will be conducted in English, which is a limitation of the systematic review.

Search strings and/or combinations of searches

Listed in Table 1.

Estimating the comprehensiveness of the search

A list of relevant papers (see Additional file 1) was used to develop search strings and test search comprehensiveness.

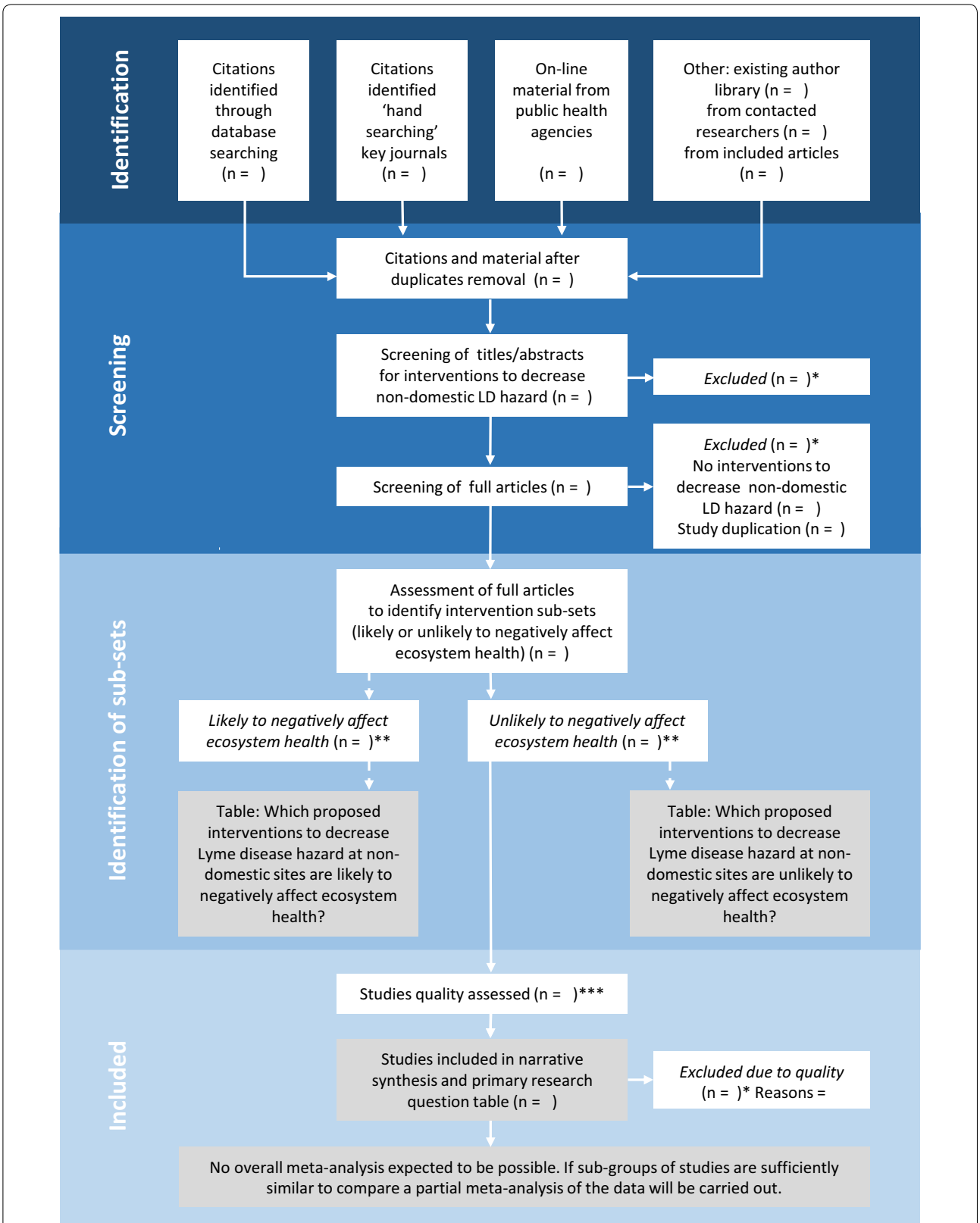

Fig. 1 LD intervention systematic review flow diagram. Outputs in *grey boxes*. Appendix to the report will include *spreadsheets with all excluded references, **assessment forms for each intervention, and ***quality assessment forms for each included study. Flow diagram adapted from PRISMA 2009 [63]

Table 1 Search terms and search strings

Databases	Search terms and strings
PubMed	"Lyme disease/prevention and control" [Mesh] OR "Borrelia infections/prevention and control" [Mesh]
Web of science Embase Global health Scopus Cochrane library	(Intervention* OR control* OR "one health" OR decreas* OR reduc* OR limit* OR prevent* OR affect* OR effect* OR lower* OR alter* OR eliminat*) AND (Lyme disease OR Lyme borreliosis OR tick-borne) AND (Borrelia OR Ixodes OR tick* OR vector* OR hazard* OR risk*)

Publication databases to be searched

Articles indexed in MEDLINE will be searched via PubMed using US National Library of Medicine controlled Medical Subject Headings (MeSH) selected using the PubMed Search Builder. Table 1 shows databases to be used. Literature will be limited to that published from 1983 onwards, the year in which *Bb* was identified as the causative agent of LD [4].

The contents of the following key journals will be examined at title level for any articles related to LD: Ecohealth, Medical and Veterinary Entomology, Parasites and Vectors, Tick and Tick-borne Diseases, Experimental and Applied Acarology, Trends in Parasitology. For practical reasons, hand searching will be restricted to journal volumes between 1/1/2010 and the time of search. Collected references will be subject to exclusions as per Fig. 1.

Internet searches to be conducted

None.

Specialist searches—searches for grey literature

Websites of the following organisations will be reviewed for public health advice, grey literature and details of unpublished or ongoing studies: Public Health England (UK), Health Protection Surveillance Centre (Ireland), European Centre for Disease Prevention and Control (EU), Centers for Disease Control and Prevention (USA), Public Health Agency (Canada), World Health Organisation (global). Where appropriate, these bodies will be contacted for further information.

Supplementary searches such as Bibliographical searches and literature provided directly by stakeholders

The reference lists of included articles will be scanned for relevant citations. Once searching and exclusions are completed, a list of included articles will be sent to established researchers in the field along with this protocol and a request for additional recommendations, including grey literature and unpublished studies. This protocol will be promoted on the University of Brighton website and advertised via social media (Twitter and Research Gate) to engage wider stakeholders and the research community. Those submitting suggestions will be offered listing in acknowledgements. References from a pre-existing library of the authors along with suggestions by others will be screened for duplication and eligibility as outlined below and illustrated in Fig. 1.

Article screening and study inclusion criteria

Screening

Screening will be carried out independently by two reviewers with spreadsheets for each set of inclusions and exclusions available as supplementary files. Identified references will be screened for eligibility first using titles, then abstracts and finally by full texts. In line with Collaboration for Environmental Evidence guidance [57], at the beginning of the title, abstract and full text screening stages a Kappa analysis using a random sample of 200 articles will be carried out to assess consistency between the reviewers in applying the inclusion and exclusion criteria. Selection criteria will be further developed and retested if the obtained Kappa rating is not 0.6 or more. Where there is a disagreement between reviewers on inclusion at full text stage a third independent reviewer will be consulted.

Inclusion criteria

Literature will be accepted for inclusion when the population involved is a non-domestic site with LD hazard, an intervention is proposed to reduce LD hazard (intervention categories listed below, in the "Relevant interventions" subsection) and the outcome measured is LD hazard (preferred outcome metric detailed in the "Relevant outcomes" subsection). Non-English language articles with English language abstracts that pass abstract level screening, will be translated and assessed for inclusion at full article stage when abstracts state the article is a report of an intervention study to reduce LD hazard. When not they will be listed in the appendix. The scoping search indicated some proposals are not backed by studies with reliable comparator data. This will be indicated following study quality assessment in the evidence synthesis step but presence of a valid comparator will not be a requirement for inclusion in the review. Similarly type of study design will not determine inclusion but will be considered during quality assessment.

Relevant subject(s) Any non-domestic sites with LD hazard worldwide.

Relevant intervention(s) Interventions proposed to reduce LD hazard, including those altering *Bb* and tick vector host community composition, vector populations, *Bb*

prevalence within vectors, site landscaping, plant community composition, and habitat structure and connectivity.

Relevant comparator(s) No intervention or an alternative intervention.

Relevant outcomes Site LD hazard. It is expected articles will quantify this differently, though density of infected nymphs (DIN) is most appropriate [58].

Relevant types of study design Any exclusions will be carried out stepwise as per Fig. 1, a filled-in copy of which will be included in the report. References that do not include interventions to decrease non-domestic LD hazard will be excluded at title, abstract and full text stages. All articles excluded at full text at any stage in the review will be listed in appendix with reasons given for their exclusion.

Study quality assessment

Study quality will be assessed using the Environmental-Risk of Bias Tool and the Environmental-GRADE Tool, adapted versions of established tools developed in healthcare research [59]. The Environmental-Risk of Bias Tool will be used to assess the risks of bias associated with each study, for example selection bias due to inadequate randomisation, and reporting bias due to selective reporting. The Environmental-GRADE Tool will be used to assess the quality of the underlying methodologies, ranging from randomised controlled trials (high quality), to case studies (low quality). Assessments will be carried out separately by two reviewers who will discuss grading differences with the intention of reaching consensus. In addition, the precision of effect estimates will be evaluated in consultation with statistical expertise. The results will be included in a table in the report.

Data extraction strategy

Data extraction will be carried out by one reviewer and forms will be used to capture the following study data when available: full reference, type of study, location, period, habitat, vector species, pathogen species, intervention, other reasons for heterogeneity (see below), methodology, sources of bias, LD hazard outcomes with mean, standard deviation and p-values, author stated key findings and recommendations for future work. A second reviewer will check the data extracted. The two reviewers will discuss any disagreements with the intention of reaching consensus. If consensus is not achieved a decision on the data to be included will be taken by a third reviewer. Where data is missing, attempts will be made to contact the authors, when practicable. All completed data extraction forms will be included in an appendix to the report.

Potential effect modifiers and reasons for heterogeneity

The following list is not exhaustive, but includes potential effect modifiers and reasons for heterogeneity which will be recorded where available.

- Outcome measure
- time between intervention and outcome measure
- sampling method
- habitat type
- vector and pathogen species
- vector and pathogen host community composition
- intervention type
- climate

Data synthesis and presentation

Identification of intervention sub-sets

Two reviewers will independently asses the included full articles to determine whether mentioned interventions would be likely or unlikely to negatively affect ecosystem health. Where there is a disagreement between reviewers a third independent reviewer will be consulted. The meaning of the concept of ecosystem health has long been contested [60]. For this review, the following summary outline will be used: 'healthy ecosystems retain vigour (productivity), resilience (capacity to recover from disturbance, indeed self-renewal), and their organization (e.g., biodiversity and symbiotic relations between species)' [61]. By this definition anthropogenic change has degraded many or most ecosystems in which humans are at risk of contracting LD. Never the less, it is anticipated that some interventions may further negatively affect ecosystem health. Forms will be developed for this step with pre-chosen evaluation criteria to judge the likely effect of interventions on: (i) vigour (measured as activity, metabolism or primary productivity), (ii) ecosystem resilience (measured in terms of a system's capacity to maintain structure and function in the presence of stress), and (iii) organisation (assessed as diversity and number of interactions between system components). See Rapport et al. [62] for further elaboration and examples of ecosystem health assessments. All forms will be available as an appendix to the report.

The cataloguing section of the report will include two tables. One will list those interventions assessed as likely to negatively affect ecosystem health. It will include a brief description of each intervention, a list of citations where it was proposed or trialled (full details in Additional file 1), and a justification of the assessment. A second table will list those interventions assessed as unlikely to negatively affect ecosystem health, and will likewise include a brief description, a justification of assessment, and a list of citations. In both tables justifications will reference evidence regarding the effect of interventions on

ecosystem health, where such evidence exists. Where it does not, justifications of assessments of likelihood will cite examples of the effects of similar interventions.

Systematic review

The systematic review will investigate the subset of interventions that would be unlikely to negatively affect ecosystem health, and determine their effectiveness at reducing LD hazard. As illustrated in Fig. 1, eligible literature will be assessed for study quality. The results will be presented in narrative, alongside tables. Given the considerable heterogeneities across studies indicated by the scoping search a full meta-analysis is not expected to be possible. However, if sub-groups of studies are sufficiently similar to enable comparison a partial meta-analysis of the data will be carried out. A table will show the data on supporting evidence for each of the interventions that were assessed as unlikely to negatively affect ecosystem health. It will include for each study involved the habitat, study type, outcome statistics and study quality grading. This table and the associated narrative synthesis will answer the primary research question: which interventions to decrease Lyme disease hazard at non-domestic sites are unlikely to negatively affect ecosystem health and what evidence exists to support their effectiveness?

Additional file

Additional file 1. Reference list used to develop search strings and test search comprehensiveness.

Abbreviations

Bb: *Borrelia burgdorferi* sensu lato; DIN: density of infected nymphs; LD: Lyme disease; MeSH: medical subject headings.

Authors' contributions

JM, IC and ASR designed the protocol and contributed to the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests. Reviewers involved in this review that are also authors of relevant articles will not be included in the decisions connected to inclusion and critical appraisal of these articles.

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