Laboratory evaluation in the diagnosis of Lyme disease


Authors' objectives
To evaluate the predictive value of laboratory diagnosis of Lyme disease and to use the resultant data to formulate guidelines for clinical diagnosis.

Searching
MEDLINE was searched from 1982 to 1996 for articles published in the English language, or with English language abstracts. The keywords used were 'Lyme disease', 'Borrelia burgdorferi', 'diagnosis', 'ELISA', 'Western blot', 'immunofluorescence assay', 'polymerase chain reaction', 'urinary antigen detection' and 'culture'. Additional references were provided by citations from authorities in the field.

Study selection
Study designs of evaluations included in the review
No study designs were specified in the inclusion criteria. The two large studies for which the data analysis was presented were case-control studies.

Specific interventions included in the review
The included studies had to provide a clear statement on the test of interest, but no specific tests to be included were specified. The included studies evaluated microbial isolation of Borrelia burgdorferi (B. burgdorferi), enzyme-linked immunosorbent assay (ELISA), Western blotting, cerebrospinal fluid ELISA, indirect immunofluorescence assay, T-cell proliferative assay for partially treated patients, polymerase chain reaction (PCR) and urinary antigen detection.

Reference standard test against which the new test was compared
The included studies had to report reproducible information on the reference standard (cases diagnosed by experts who were blinded to the results of the diagnostic tests being evaluated).

Participants included in the review
The included studies had to report reproducible information on the sampling and clinical details of patients with the disease, as defined by the US Lyme disease national surveillance case definition, and study controls. Studies describing results in patients outside North America were excluded because of systematic differences in strains of B. burgdorferi in different parts of the world. No other information on the participants was provided.

Outcomes assessed in the review
The included studies had to report sufficient information to permit the calculation of sensitivity and specificity. The outcomes calculated and reported in the review were the sensitivity, specificity and positive and negative likelihood ratios (LRs).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using guidelines developed for evaluating diagnostic tests by meta-analysis (see Other Publications of Related Interest no. 1). The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
Methods of synthesis
How were the studies combined?
The sensitivity, specificity and LRs were calculated for individual studies, while a random-effects model was used to combine the proportions from the eligible studies.

How were differences between studies investigated?
No tests for heterogeneity were performed, although differences in the studies were discussed.

Results of the review
Eight studies evaluating serologic testing met the inclusion criteria. Two studies, involving 262 patients with Lyme disease and 252 controls, evaluated ELISA. Four studies with an unreported number of participants evaluated Western blotting. Two further studies with an unreported number of participants evaluated indirect immunofluorescence assay.

No studies met the inclusion criteria for assessing the diagnostic effectiveness of microbial isolation of B. burgdorferi, cerebrospinal fluid ELISA, PCR and urinary antigen detection.

Two studies were included in the assessment of the sensitivity, specificity and LRs of serologic ELISA. In early Lyme disease, the random-effects combined estimates were 59% for sensitivity and 93% for specificity, with positive and negative LRs of 8.42 and 0.44, respectively. For late Lyme disease, the random-effects combined estimates were 95% for sensitivity and 81% for specificity, with positive and negative LRs of 5.01 and 0.06, respectively. These indicate that if the patient has clinical symptoms and signs that are consistent with Lyme disease (a pre-test probability that exceeds 0.20), the information provided by ELISA is clinically useful. If the result is positive the disease is ruled in, and if the result is negative the disease is ruled out. In non-specific clinical presentations, testing is more likely to mislead than to help establish the correct diagnosis.

Four studies were included in the assessment of Western blotting. The criteria used by these studies to designate a positive result varied considerably. Two of these studies showed that Western blotting was useful in adding information to positive or indeterminate ELISA tests. The combined positive LR for indeterminate results from ELISA alone was 1.05. The addition of positive Western blot results increased the combined positive LR to 11.7, while the addition of negative Western blots to negative or indeterminate ELISA resulted in a combined negative LR of 0.08. In effect, in indeterminate results using ELISA, where the probability of disease has increased from 0.50 pre-test to 0.51 post-test, the addition of a positive Western blot increases the probability to 0.92.

Two studies were included that examined indirect immunofluorescence assay; this technique showed similar sensitivity and specificity to ELISA.

Cost information
A cost-effectiveness analysis was referred to, but was actually undertaken in another paper (see Other Publications of Related Interest no. 2).

Authors' conclusions
Laboratory testing, using ELISA or immunofluorescence backed up by Western blot for indeterminate cases, is recommended only in patients whose pre-test probability of Lyme disease is 0.20 to 0.80. If the pre-test probability is less than 0.20, testing will result in more false-positive results than true-positive results; a negative test result in this situation effectively rules out the disease.

CRD commentary
The authors of the review provided adequate description of the objectives of the review, the interventions included, the
outcomes assessed, the inclusion criteria and the sources searched. The search strategy was limited and may have missed relevant studies. The possibility of publication bias was not addressed and no attempt to identify unpublished studies was reported. There was limited information on the participants, study designs and other details of the primary studies, although methodological quality formed part of the inclusion criteria. The description of the review methodology was poor, leaving open the possibility of bias introduced by flawed review processes. The presentation of the results was somewhat confused, with excluded studies being described under some sections. In the one instance where pooling was undertaken, heterogeneity was not formally assessed or considered in any detail and, since only two studies were involved, would seem to have very limited value.

The authors' conclusions follow broadly from the data presented. However, the conclusions were based on the findings of only two studies. This, in addition to the limitations outlined already, indicates that the conclusions should be viewed with some caution.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.