Reviewer's report

Title: Diagnostic behaviour of general practitioners when suspecting Lyme disease: a database study from 2010-2015

Version: 0 Date: 21 Aug 2017

Reviewer: Agnetha Hofhuis

Reviewer's report:
I agree with the authors of "Diagnostic behaviour of general practitioners when suspecting Lyme disease: a database study from 2010-2015" that the overuse of serology for Lyme borreliosis and consequently overtreatment with antibiotics needs to be addressed internationally. This database study must have cost a lot of working hours. Publication of these study outcomes can raise awareness and possibly aid development of solutions. I think that this paper has merit, provided that the authors substantially improve the information about the dataset and implement up-to-date literature into their introduction and discussion. Please see my detailed comments below.

Specific comments:
Throughout the manuscript it is acknowledged that the main outcomes - how many times serological testing was performed, and proportion of positive test outcomes - rely on the way that data was collected. I assume that serological testing was performed for 100% of the consultations that were included in this database study through one of the 16 diagnostic test codes for Lyme borreliosis. Therefore, it is most relevant to report the number (and %) of records solely included through a serological testing code. To clarify the origin of the 2,311 consultations, I strongly recommend that the authors present the numbers and % of records yielded through each search term and code from the appendix table, and incorporate it into figure 1. In addition to that, this is a great opportunity to evaluate the applicability of ICPC data for study or surveillance purposes, and the added value (how many were not found through ICPC) of the other search terms and the serological testing codes. As an epidemiologist, I would greatly appreciate some information on the overlap of the three main searching strategies.
Page 6 line 153 on strengths and weaknesses: Having generated the above numbers. Please elaborate more on how your data selection influenced your outcomes.

The background and discussion contain statements based on outdated and sometimes irrelevant literature.
e.g. the EUCALB website (reference 5 AND 12!) is no longer online.

Page 3 line 54 is incorrect, as mosquito borne diseases are the most common vector borne diseases worldwide. Please change to "Lyme Borreliosis (LB) is the most common tick-borne disease in the world" or "Lyme borreliosis is the most common tick-borne infectious disease in North America and in countries with moderate climates in Eurasia."
Reference 1, 2, 3 do not substantiate this.

Instead refer to for instance:

Page 3 line 55 "of which Borrelia afzellii and Borrelia garinii are most prevalent in Europe [4-7]."
This is not substantiated by reference 5 and 6

Page 3 line 60 - 61: ref 12 is no longer online and ref 14 is USA, so not a European guideline. Please add references on European guidelines.
Furthermore: "This high a priori probability is mainly based on symptoms (like arthritis or neurological symptoms)" It may be helpful throughout the whole manuscript, if you distinguish between "LB-specific" symptoms and "non-characteristic" symptoms.
Page 3 line 63, and Page 6 line 149: "since a substantial percentage of the general population is seropositive for LB."
This is about IgG. Please specify "substantial" and add a reference on the prevalence of anti-borrelia-IgG in the Netherlands.

Page 3 line 64: "This is because serological tests do not differentiate between an active LB and an (asymptomatic) infection from the past [10]."
You make it sound as if serology is useless. Specifically when disseminated Lyme borreliaosis presents with non-characteristic manifestations, the uncertainties of imperfect laboratory diagnostics present a diagnostic challenge. Misdiagnosis based on non-characteristic symptoms, combined with false positive serologic test results is common, so patients with medically unexplained symptoms, and others with more well-defined disorders, are wrongly diagnosed with Lyme-related persisting symptoms. Please read and refer to

Page 3 line 65: "The seropositivity rates for LB vary throughout Europe, from 3.4% in the
general population in Italy to 66 15.2% in France [15]. " Incomplete information which reference
15 does not substantiate. I suggest to read and refer to Hubalek Z: Epidemiology of lyme
And to mention that the incidence of Lyme borreliosis in Europe shows an increasing gradient
from west to east with the highest incidences in central-eastern Europe, and a decreasing gradient
from south to north in Scandinavia and from north to south in Italy, Spain and Greece.

erythema migrans is written without capitals.

Abstract Page 1 line 43. Please specify the years instead of "over time"

Page 1 line 44 on "The general practices in our study showed considerable differences with
respect to serological testing." Please revise so that it becomes more clear that you mean the
differences between the practices.

Please revise line 86 on page 4: "Contacts with not related to…"

Page 4 line 104: "Chi-square tests for trend (linear-by-linear) were used for
105 comparing differences between years regarding contacts, episodes and serological tests."
Was this also used for comparison of testing numbers per GP practice?

Results Page 5 line 114:
"The overall incidence of episodes related to LB was 8.8/1000/year." To be clear, I suggest to
write "8.8 per 1000 person years within the dataset of 56,996 ".

Table 2
Heading reads "registered symptoms" but table includes "diagnostic and therapeutic requests"
Maybe change heading to "reasons for consultation / contact" ?
"IV Diagnostic therapeuric requests" puzzled me for a while. Please clarify that this is about
requests made directly by the patient.
Categories "Other" consist a large number of consultations, about a fifth of "1 General symptoms" and of "VI skin abnormality". Please add a * and subscript with the top 5 (n, %) of the most frequently reported symptoms in these "other" categories.

"Doubt erythema migrans" does not seem English to me.

Page 5 line 128:
"The percentage of positive test results was highest for the 129 episodes in which patients presented with skin abnormalities (14.5%) …" Could you please also provide this information for the EM group and the non-EM group separately? And include this in table 2.

Page 5 line 130:
Please add the denominators: 19.1% is 26/136, right?
9.5% is 31 / ?? of the episodes in which patients presented with asymptomatic tick bites. It would be nice to see these numbers also in table 2.

Page 6 line 145 & page 7 line 175 & page 8 line 202:
Symptoms such as fatigue headache and arthralgia are wide spread but real. They are however not specific for LB. Consider to rephrase the "non specific complaints" as "non specific for LB". check this throughout the manuscript.

Page 6 line 151: "2010 and 2015" should probably be "2010 to 2015"

Page 7 line 160: "because we did not only rely on ICPC-codes but also included the free text annotations which were mined on relevant search terms." Shouldn't the diagnostic testing codes be mentioned here? They were used to find more consultations on LB, right?

Page 7 line 167: "Given the low percentage of seropositive patients (5.9%) in our study population, …"
Combined with the symptoms being not specific for LB, right?
For example, an Australian study showed that 64.2% of patients presenting with received laboratory testing" Presenting with …what?

The large differences in serological testing between general practices showed that there is no consensus when to perform serological testing on LB in general practice." But there is consensus. Read the guidelines. However, the physicians need to be aware and apply the guidelines.

Page 8 line 188: Implications for clinicians and research
I agree that physicians need to be aware of how to deal with the uncertainties of laboratory diagnostic tests, when (not) to test, and when to refer a patient for diagnosis by a medical specialist in the hospital. Please elaborate on your idea of an algorithm to diminish unnecessary serological testing.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:
Needs some language corrections before being published
Declaration of competing interests

Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?
5. Do you have any other financial competing interests?
6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal