Author’s response to reviews

Title: The HUMTICK study: Protocol for a prospective cohort study on Post-Treatment Lyme Disease Syndrome and the disease and cost burden of Lyme borreliosis in Belgium.

Authors:

Laurence Geebelen (laurence.geebelen@wiv-isp.be)
Tinne Lernout (Tinne.Lernout@wiv-isp.be)
Benoît Kabamba-Mukadi (benoit.kabamba@uclouvain.be)
Veroniek Saegeman (veroniek.saegeman@uzleuven.be)
Hein Sprong (Hein.Sprong@rivm.nl)
Steven Van Gucht (Steven.VanGucht@wiv-isp.be)
Philippe Beutels (philippe.beutels@uantwerpen.be)
Niko Speybroeck (niko.speybroeck@uclouvain.be)
Katrien Tersago (Katrien.tersago@wiv-isp.be)

Version: 1 Date: 27 Apr 2017

Author’s response to reviews:

Dear editor, Dear reviewer,

We thank you for the comments on the manuscript. We tried to address all the comments suggested by the reviewer. Revision details are listed below (in blue), in addition, changes were highlighted in track changes in the manuscript.

Reviewer reports:

Reviewer #1: Geebelen et al. proposed a paper entitled: « The HUMTICK study: Protocol for a prospective cohort study on Post-Treatment Lyme Disease Syndrome and the disease and cost burden of Lyme borreliosis in Belgium ». This is the protocol of a very ambitious study aiming to evaluate the incidence and possible risk factors to develop PTLDS and to estimate the disease and cost burden of borreliosis in Belgium. This will be a very interesting study that will bring
new knowledge on borreliosis disease. I think that after some improvement of the method section, which I find not detailed enough, the paper would be acceptable for publication. I also would like to review the questionnaire (not SF-36, CFQ, EQ5D, GALI) that will be used to collect the risk factors, comorbidity, tick-bite exposure, prescribed treatment…, because it is not available in the supplementary appendix.

Answers to general comments:

The method section has been adapted according to the specific comments. As this study is designed specifically for the Belgian population, the questionnaires are only available in Dutch and French. As an example, the questionnaire for EM is now uploaded. In total there are 9 different questionnaires (an inclusion, 1 month follow-up and 3(=6/12/24) month follow-up questionnaire, partially different for sub-cohort 1 and 2, a GP follow-up questionnaire and 2 control group questionnaires), in two languages, counting around 230 pages in total (including validated questionnaires). We therefore consider that it is too much to add as an appendix. However the questionnaires can be provided on demand by the corresponding author.

Answers to specific comments:

L8 (p2): "Lyme borreliosis…".

I would "add and having been treated?"

Having been treated is included in the definition of PTLDS and therefore not added here but described in the previous sentence. To make it more clear changes are made to the manuscript: “Despite recommended antibiotic treatment, a proportion of Lyme patients report persisting aspecific symptoms for six months or more (e.g. fatigue, widespread musculoskeletal pain or cognitive difficulties), a syndrome now named “Post Treatment Lyme Disease Syndrome” (PTLDS).”

L6 (p3): "a red expanding rash…".

I would explain what the risk factors for having an expanding red rash are. I suppose it would depend for instance on the location of the bite or on the time the tick remained hanging.

The duration of the tick’s blood meal (time of tick attachment) is indeed, together with the tick infection rate, a risk factor, not for the development of an EM but in general for transmission of the bacteria and so for acquiring a Borrelia infection (asymptomatic, EM or disseminated Lyme) after a tick-bite. Although this is definitely an interesting subject, we decided not to include it in our paper since our focus is on the manifestations of Lyme and the development of PTLDS after a Lyme borreliosis diagnosis and not on the development of
Lyme borreliosis after a tick-bite (on which more complete literature exists). We did make some changes to the background to clarify the lines about symptomatic infections and the possibility of an asymptomatic infections.

L9 (p3): "If left untreated…".

How do you define the treatment? I mean is the tick removal a treatment?

- Here we refer to when infection already took place and so untreated refers to not getting a treatment with antibiotics. Changed in manuscript: “If an infection is not treated with appropriate antibiotics, it can possibly evolve to disseminated…”

I would also better explain that some people may be bitten, have a red rash, remove the tick and never developed disseminated Lyme borreliosis.

- See changes above “…can possibly …”

- As explained above, we want to avoid making the introduction too long, and therefore we’ve chosen to limit the information to what is essential for understanding the study.

Do you have any ideas of the risk factors linked with disseminated Lyme borreliosis (very young children, immunocompromised people, season,…)?

- There is not much known about risk factors specific for the development of disseminated Lyme borreliosis. In theory immunocompromised people would have a greater risk on developing disseminated Lyme borreliosis but this hypothesis is not always confirmed by the limited research done in humans and therefore not mentioned in our manuscript. In our study all patients are asked whether they have immunodeficiency (due to disease or medication) so this can be taken into account in further analysis.

L13 (p3): "Cognitive difficulties".

This concept seems very broad, maybe it would be useful to give an example.

- Changed in manuscript: “fatigue, widespread musculoskeletal pain or cognitive difficulties (e.g. memory problems, difficulties concentrating, problems finding words)."
L18 (p3): "Incidence estimation…".

Is "incidence" the correct term?

Where this incidence come from? Belgium? Europe? I would be more specific.

- This range comes from a review by Koedel et al. (2015), this is now specified in the manuscript. It is based on literature from both north-America and Europe (so not specific for one of both areas where Lyme is most prevalent and therefore not specified). Incidence is indeed not the correct term to use here.

- This is now changed in the article as “A review by Koedel et al. (2015) reported that PTLDS symptoms developed in 5-54 % of Lyme patients that suffered from Lyme neuroborreliosis. [15].”

L10 (p4): "." To be deleted

- Deleted, thank you.

L16 (p4): "been assessed". Has the burden of borreliosis already been assessed by other countries?

- Yes, the burden has been estimated in the Netherlands. This is mentioned in the discussion (page 13, line 10 in final document): “A study in the Netherlands did estimate the disease burden for Lyme borreliosis and found that the majority of the substantial burden is caused by persisting symptoms [59].”

L20 (p5): I would add "Having already suffered of borreliosis" as an exclusion criteria.

- This is indeed something we have to take into account but it is not added as an exclusion criterion for participation in the study. We do ask all patients to report previous borreliosis episodes (diagnosed by a doctor). As such, potential previous Lyme borreliosis episodes can be excluded from the analysis of the development of PTLDS in relation to co-infection, alternatively, the dataset still allows evaluation of previous Lyme borreliosis episodes as a risk factor for PTLDS. Also, since the study already started, it is not possible anymore to change the exclusion criteria.
L3 (p6): Will be? (June 2016) Has the study already started?

- The inclusion of patients in the study indeed already started.
- Changed in the manuscript: “Participants are enrolled since June 2016 and up to August 2018 with…”

L6 (p7): Would it be possible to have access to the formula/code you used for the sample size calculation? I don't find exactly the same results as you. Thank you!

- Yes, the sample sizes are calculated using the pwr package in R (pwr.2p.test in the cohorts and pwr.2p2n.test in the case-control), you find the R code used below:

Cohort 1 (EM patients):
Assumption = 12.5% of EM patients develops PTLDS (p1=0.125) and 5% of Non-Lyme controls develop the same symptoms: (p2=0.05)

```r
> ES.h(0.125, 0.05)
[1] 0.2717074

> pwr.2p.test(h=0.2717074, n=NULL, sig.level=0.05, power=0.90, alternative="two.sided")
sig.level = 0.05,
Difference of proportion power calculation for binomial distribution (arcsine transformation)
h = 0.2717074
n = 284.6578
sig.level = 0.05
power = 0.9
alternative = two.sided
NOTE: same sample sizes
```
Cohort 2 (disseminated Lyme patients):

Assumption = 20 % of Disseminated Lyme patients develop PTLDS (p1=0.20) and 5% of Non-Lyme controls develop same symptoms (p2=0.05):

> ES.h(0.20, 0.05)

[1] 0.4762684

> pwr.2p.test(h=0.4762684, n=NULL, sig.level=0.05, power=0.90, alternative="two.sided")

Difference of proportion binomial distribution (arcsine power calculation for transformation)

h = 0.4762684
n = 92.64511
sig.level = 0.05
power = 0.9
alternative = two.sided

NOTE: same sample sizes

92 is changed in the manuscript to 93!

Case-control study set-up within cohort 1

(to analyze the association between PTLDS and co-infections as a risk factor)

Ratio cases-controls = 1:2

Assumption = less than medium effect size: h=0.4
> i<-2
> while(pwr.2p2n.test(h=.40, n1=i,
  n2=i*2)$power < .80) {i <- i + 1}
> pwr.2p2n.test(h=.40, n1=i, n2=i*2)

difference of proportion power calculation for binomial distribution (arcsine transformation)

h = 0.4
n1 = 74
n2 = 148
sig.level = 0.05
power = 0.8022115
alternative = two.sided

NOTE: different sample sizes

L17-18 (p7): Would it be a printed questionnaire?
Will the "follow-up" questionnaires be sent by email? Or it will be a face to face interview?
This is not well explained.

- The first questionnaire is a printed version, the follow-up questionnaires are send by email, or by post if requested by the patient in the first questionnaire. This was indeed not well explained and more details on the different questionnaires are now added to the manuscript. Thank you.

L6 (p9): To my knowledge, there are no Belgian tariff for EQ-5D-5L (only for 3L and only based on Flemish population).

- Here we are referring to the population norms collected through the Belgian national health interview survey 2013 (10,829 Participants) in which the EQ-5D-5L was integrated. I added the reports as references in the manuscript.
L15 (p9): Could you describe which socio-demographic variables you plan to collect?

- Changed in manuscript: “To identify possible risk factors for the development of PTLDS, information on comorbidity, tick-bite exposure, severity and duration of symptoms presented, prescribed treatment (type, duration) as well as socio-demographic variables (age, sex, education, employment) will be collected during the complete study.”

L21 (p9): + severity + occurrence + duration…

"The latter is calculated based on incidences".

I would correct the sentence. The latter is calculated based on incidences if incidence-approach is used (which is commonly the case in burden of infectious diseases estimates). If you are using prevalence approach, then morbidity is calculated on prevalence data. I found the burden paragraph not detailed enough.

- The sentence is changed and more details on the DALY calculation are added to the paragraph in the manuscript. It is indeed an incidence approach that will be used.

L1 (p10): How do you plan to translate 5L into 3L (as no tariff for 5L are available)?

- The scores of the 5L will first be transformed into 3L scores, using the EuroQol crosswalk method described in the EQ-5D-5L user guide, the existing 3L tariff developed by Cleemput et al. will then be used to translate the 3L score into utilities. This is now, in short, described in the manuscript and the references to the user guide and Belgian tariff are added.

How do you plan to translate utilities from EQ-5D-5L to DW?

- To obtain the DWs we will calculate the difference between the participants’ utilities and the age and sex adjusted EQ-5D population averages for Belgium (most recent data available at the moment of analysis will be used, data published by Bilcke J et al (2017) or based on the Belgian Health Interview Survey 2013). This way we can take into account other comorbidity and we will have the DWs specifically attributed to Lyme borreliosis. Paragraph changed in manuscript.

How do you plan to merge questionnaire and VAS answers?
The DW’s will be calculated through the questionnaire scoring (EQ-5D-5L) only. Since the euroqol doesn’t allow use of the questionnaire without using the VAS, the VAS is added in the patients’ questionnaires but these will not be used for the DW calculation. This wasn’t described clearly in the manuscript so changes are made. Thank you.

L6 (p10): How do you plan to calculate the YLLs?

Do you expect some mortality rate linked with borreliosis disease?

We don’t expect any mortality since no Lyme related deaths have been reported in Belgium between 1998 and 2014 (only data available) therefore YLLs will equal zero. This is now added to the paragraph: “Since Lyme related mortality is exceptional and no Lyme related deaths have been reported in Belgium between 1998 and 2014 (only data available) YLLs will equal zero.”

If so, which life expectancy table do you plan to use? Do you plan to perform a time-discounting? Or age weighting? + justify your choices, thank you!

Not applicable

I found the burden paragraph not detailed enough.

More details are added in the paragraph.

L10 (p10): I don't understand the link between the minimization of recall bias and the cost diary. Could you better explain?

Since patients receive a follow-up questionnaire at 1 month, 3 months, 6 months, 12 months and 24 months after inclusion in the study, some time passes between consecutive questionnaires and recall periods take up to 12 months at the end of the study. Therefore patients are invited to note their costs in between consecutive questionnaires in the cost diary and to use the diary when filling in a new questionnaire. The explanation is changed in the manuscript: “To minimize recall bias between two consecutive questionnaires (recall periods up to 12 months at the end of the follow-up period), patients are invited to keep a cost diary during the complete study period.”

I would be clearer in the "Costs" paragraph. I don't understand how you will merge the answers of the participants regarding the 'direct medical costs' with the data you will collect from official
sources, what is the interest to have two data sources for direct costs? Do you plan to attribute more weight to "official" sources than to participant's answers?

- The official sources will provide different information in addition to the questionnaires (so we will not attribute more weight to either one of them): the questionnaires collect data on how often which direct medical costs are incurred by the patients (e.g. how many visits to a GP/specialist/physiotherapist/…, which medication is used, how often is it used,…). Official databases will be used to know the exact standard cost (e.g. the price of the medication prescribed/ of a consultation with a GP/ of a laboratory test,…). The paragraph in the manuscript is now changed in order to explain this better.

L23 (p10): On which confounding variables you're expecting to adjust your model?

- The multivariate regression models used to calculate the exposure risk ratios and the odds ratio of the risk factors will be adjusted for age, gender and comorbid illness as potential confounding variables. The conditional log-binomial regression model used to compare the development of the non-specific disease symptoms between the cohorts and the “matched” non-Lyme borreliosis control group will be adjusted for comorbid illness only since these groups are already matched for age and gender. Changed in manuscript “A conditional log-binomial regression model with adjustment for comorbid illness will be used to compare the development of the ….” Changed in manuscript: “The multivariate models will include adjustment for potential confounding variables (age, gender and comorbid illness).”