**Author's response to reviews**

**Title:** Syphilis epidemiology in Norway, 1992-2008: resurgence among men who have sex with men

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**Author's response to reviews:** see over
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Title: Syphilis epidemiology in Norway, 1992-2008: resurgence among men who have sex with men

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Dear Ms Rajabi,

We found the reviewers’ comments useful and have revised the manuscript describing syphilis epidemiology in Norway from 1992-2008 accordingly. Below is a point-by-point response to the reviewers’ comments. The revisions are highlighted in the manuscript.

We are submitting the new version of the manuscript through your webpage and we hope that it will be now accepted for publication.

Looking forward to hearing from you soon.

Sincerely yours,

Irena Jakopanec
Reviewer Jorge Sanchez:

Minor essential revisions:
Figure 2 does not add much information and HIV coinfection could just be more explain in the text.

Response: In the context of recent focus on STI and HIV co-infection among MSM, we find the figure useful to present these trends. We also point out that other reviewers did not suggest removing this figure.

Reviewer David Templeton (changes in manuscript highlighted in yellow):

1. What is unclear and requires clarification in methods section is how notifiers know that the infection was acquired within the previous year if the patient is asymptomatic. This is especially relevant to the results section "Women" paragraph: "Women seem to be more frequently diagnosed as late as the early latent stage". How was early latent syphilis defined? By definition this is syphilis infection acquired within 1 year (i.e. a documented negative test within 1 year of the current test) and no symptoms or signs of syphilis. This means that each individual categorised as early latent syphilis would have to have a documented negative syphilis test within the previous year. The text does not state if this is the case. Unless these criteria are satisfied, the authors cannot attribute a proportion of syphilis diagnoses as being in the early latent stage and this would be a major limitation of the current analysis. The methods section states "First positive syphilis tests" are notified, so it appears that no previous syphilis test result would be available, making the diagnosis of early latent syphilis in an asymptomatic individual impossible.

Response: We agree with the reviewer this needs to be further addressed in the manuscript. The classification of cases is based on what the clinicians report on the notification form and in many cases on our subsequent dialogue with them. For homosexually acquired cases a clinician will often have a previous negative test which makes it easy to classify correctly. For heterosexually acquired cases the classification is most often based on the case history, especially a clear history of risk exposure. As syphilis is such a rare disease among heterosexuals in Norway, infection can usually and reasonably be attributed to a specific exposure, for example sex with a prostitute in Asia. We agree that these classifications have some limitations. We have now explained the surveillance system and our routines in the methods in detail and pointed out these limitations in the background and discussion.

2. the length should be substantially reduced prior to publication (especially the introduction and discussion sections). The first 3 paragraphs of the introduction could be condensed into a brief 3-4 line summary of syphilis rather than detailing the natural history which is not of particular relevance to this paper. The discussion is also unnecessarily long.
Response: We have shortened the description of the natural history of syphilis and tried to structure the introduction better, but the epidemiology of syphilis in other countries was added, due to a comment of another reviewer. The discussion was shortened as you suggested in the following comments, however the limitations of the study were described in more detail.

3. Abstract, results: were no cases at all diagnosed in MSM in 1992-94? Could another explanation of the huge increases in early syphilis among MSM and other populations be that the notifications system has improved or that sexual behaviour reporting has improved?

Response: Yes, no cases were reported in 1992-1994 and hardly any (3) before an increase in 1999. This was now emphasized in the results. There have been no changes in the notification system, especially not on reporting of transmission category, which could explain these changes. Please, see discussion.

4. Paragraph 2: 'could the authors please clarify the sentence "A single co-existent STI can be reported with HIV as a priority"'? I had to read this several times before I realised what was meant. Suggest change to: "Data on co-existing STIs is collected, however, only one other STI can be reported on data collection forms. If the patient also has HIV, notification of their HIV diagnosis as the co-existing STI is prioritised"

Response: We have made suggested correction according to our actual routines.

5. Paragraph 3: "For the purpose of this study, we denoted men who had been infected with syphilis by another man "men having sex with men" (MSM). Could the authors please clarify this further. What is the specific question asked of clinicians regarding gender of partners? For example is it any sex with men, over a specific time period? i.e. can the authors categorically state that syphilis was acquired by MSM contact based on the data reported by clinicians?

Response: The notification form asks the notifier to specify the “most likely transmission route”, and one of the choices is “homosexual transmission”. The reviewer is right in pointing out that we do not know how the patient would describe himself, only how transmission of the infection happened. We believe most clinicians get sincere answers to questions on sexual behaviour in Norway. We have now decided to use more appropriate term “homosexually acquired syphilis”, but refer to MSM in the discussion.

6. Results:
Paragraph 2: please state "p-trend" if the statistical test applied (average 3.8 cases/year increase) was a test for trend and "95% CI" rather than only "CI"
MSM paragraph, line 5, "most of the cases" would have to be >50%, not 43%
Line 6/7: The proportion of HIV co-infected increased [add: over time] and state p-trend <0.001

Response: We made changes as suggested and used the term “p for trend".
7. Men infected heterosexually paragraph:
"No obvious time trend was observed": please state p-trend value for the reader
"More than half was older...." should read "were older"
"Women" paragraph, line 1: remove comma after "Among 56 women"

Response: The suggested corrections were made.

8. Table one: Please indicate whether p-values are p for trend (i.e. age) or p for heterogeneity (i.e. birthplace)

Response: All p values in the table are for heterogeneity, a comment was added.

9. Table two could be removed and the finding briefly stated in the text, as it adds little to the paper

Response: The suggested replacement with the text was made.

10. Discussion: Paragraph one, line 2: "...MSM, including HIV positive" suggest changing to "....disproportionately affecting HIV positive" as one-quarter had HIV

Response: The suggested corrections were made.

11. Paragraph one, line 3-4 (and results section "Women" paragraph): "Women seem to be more frequently diagnosed as late as the early latent stage". This is unclear. More frequently diagnosed than who? And how was early latent syphilis defined? (see earlier comment)

Response: The suggested clarifications were made.

12. "get infected" line 3, paragraph one and elsewhere in discussion is too strong a phrase as the risk factors are based on limited behavioural data. Suggest changing to "appear to be infected by", "reported being infected by" or "were likely to have been infected by"

Response: The suggested corrections were made.

12. Prostitutes: should be changed throughout the text to "sex workers" which is now the accepted terminology

Response: Corrections were made in the text and the table to “commercial sex workers”.

13. Paragraph 3, 3rd sentence: "each year about 100 cases are reported by laboratories, but not clinicians". The authors include 562 early or congenital cases over a 16-year period notified. However, by my calculations, 100 cases a year equates to 1600 cases during the study period which would be three quarters of all syphilis cases diagnosed in Norway during this time period. Obviously the limited information on these presumed late latent cases precludes further analysis, but the large majority of syphilis cases diagnosed late is notable
and deserves further comment

Response: We believe these notifications of serological findings either represent previously treated disease, or late latent, tertiary or unknown stage. We agree this must be further addressed in the manuscript. Additional explanation has been added in the discussion. Proportions of late syphilis from three other European countries (with universal case reporting) in the recent years were calculated and added for comparison. Further comment on this issue was added as additional paragraph at the end of the discussion.

14. Paragraph 7 could be removed as the 4 cases of congenital syphilis, 2 of which were in adopted children from abroad is not noteworthy (except to say that it is very rare in Norway)

Response: Paragraph 7 was removed.

15. Paragraph 8&9 deal with oral sex as a possible risk factor for syphilis acquisition. Although this is noteworthy and probably accounts for a substantial minority of syphilis infections in MSM (see Jin et al. Med J Aust 2005; 183 (4): 179-183) condoms use for oral sex among MSM is very rare in all settings and reference to low condom use for oral sex could be removed. Paragraph 8 is confusing to read and requires clarification. Could the fact that more heterosexual men than MSM are diagnosed in the primary stage reflect the chancre being painless, and therefore more likely to pass un-noticed in anal or oral areas among MSM, compared with penile chancres in heterosexuals? The authors could comment on this.

Response: We find these suggestions very useful. Paragraph 9 was removed. Paragraph 8 was rewritten and explanation on unnoticed chancre in anal or oral areas has been added.

16. Paragraphs 10-13 could be condensed to one short paragraph briefly outlining the contents of table 2 and concluding that overseas sexual contact is a key risk factor for heterosexually-acquired syphilis in Norway. That is the important message here and does not require so much discussion.

Response: We agree with your comment and have shortened these paragraphs into a single one.

17. Paragraph 14 does not add to the discussion and should be removed

Response: We removed this paragraph.

18. Paragraph 15 regarding frequency of testing to control syphilis among MSM and HIV positive is of key importance. Suggest keeping from line 2 "An evaluation..." to " ideally 2-4- times a year" and putting in final conclusion paragraph.

Response: Suggested changes were made.

19. **Quality of written English**: Needs some language corrections before being
Response: We invited a native speaker to review the language.

Reviewer Asuncion Diaz (changes in manuscript highlighted in green):

Are the methods appropriate and well described? Yes, although some information is missing. For instance the Norwegian surveillance system needs better description.

Response: The surveillance system was explained in more detail.

Major Compulsory Revisions:

1. Background:
I would suggest reducing the first two paragraphs since the main clinical features of syphilis are well-known to the potential readers. On the other hand, the authors should include some data on syphilis epidemiology in Europe: recent trends, resurgence among MSM in other countries etc. to help the reader to understand the reasons for writing this paper.
Final paragraph of the introduction (page 5): please, re-write the purpose of the manuscript. Stratification variables should be described in the Methods section.

Response: We reduced the paragraphs on natural history of syphilis and added a short description of syphilis epidemiology of Europe (also in the abstract), together with general trends among MSM and HIV co-infection. Stratification variables were removed from background.

2. Methods:
Please, re-order this section. My suggestion would be to put the first paragraph at the end, together with the data analysis. Also, in the last paragraph it should be mentioned that the 95% confidence intervals for incidence rates are presented.
Some more information about the syphilis surveillance system in Norway is needed: is it voluntary or mandatory?. Is it mandatory only for the laboratories or also for the clinicians?
Please provide a syphilis case definition.
Second paragraph: “Clinicians fill out the clinical report with data about partner of index case”. Is partner notification compulsory in Norway?
Second paragraph: Is HIV testing mandatory for all syphilis cases?
Third paragraph: MSM co-infected with HIV are compared with those not co-infected. Why the same is not done for heterosexual people?

Response: Suggested adjustments, clarifications and restructuring were made in the Methods. We have explained previously that 95 % confidence intervals were obtained using Newey-West procedure and do not find it necessary to repeat this separately for incidence rates. Information on HIV co-infections as an emerging problem among MSM, infected with syphilis, was added to the background. We did not notice this problem among heterosexuals and I would like to point out that, as presented in Table 1, only 3 heterosexual persons were HIV co-infected.
3. Results:
Page 7, line 3: “but in 1999, a marked increase with 40 cases occurred (75% of all cases)...” Please, clarify this percentage: is 75% of all cases in 1999 or 75% of all cases in the study period?.

Response: Suggested clarifications were made.

4. Page 7, line 7: “The proportion of HIV co-infected increase (p<0.001) and reached 39% in 2008 (Fig. 2). Please, provide information about the first year of the comparison period.

Response: Please note there was no comparison period, but we calculated the trend throughout the study period. In addition, trend was now also calculated from 1999.

5. Why data about HIV/syphilis co-infection from 1992 to 1997 are not presented?. Is this because no HIV- infected syphilis cases were found or because not all syphilis cases were HIV tested during the study period?

Response: Figure 2 represents data on homosexually acquired syphilis (and HIV co-infected cases in this group). We have now emphasized in the results that only 1 homosexually acquired case was reported in 1995 and 2 in 1998.

6. Page 7, line 11: “being diagnosed with syphilis in later stages (p=0.006)…” What does “later stages” mean?

Response: We have now clarified this sentence.

7. Page 8, line 5: “Symptoms were the cause of testing in 27% cases and pregnancy in 23%”. However, in table 1 it is clear that most women were diagnosed due to contact tracing (30%); I think it is important to underline this fact.

Response: This is a good suggestion and we have made changes accordingly.

8. Table 1. Some categories in several variables have very few cases. I wonder whether the Fisher’s exact test would not be preferable to the chi-square test in these instances.

Response: We did not recalculate the results according to this suggestion. We would like to point out that Fisher’s exact test is designed for two by two tables. We believe our results would not be importantly affected if we would choose Fisher’s exact test.

9. Discussion:
First paragraph: “Since 1999, there has been resurgence among MSM, including HIV positive”. Has there been any syphilis outbreak among MSM during the study period?. Because if this were the case, it is possible that the increasing incidence was due to the outbreaks.
Response: As most of the cases occur in Oslo, we tend to regard the whole resurgence as one large long-lasting outbreak.

10. Second paragraph: The authors comment that a strength of this study is the high coverage of the surveillance system. Could they provide information on coverage in the Methods section?

Response: Although the assumed coverage is high, the greatest limitation in our system is selection of “early syphilis cases only” to be entered into the surveillance system. The effect of actual coverage on our data is difficult to evaluate, as we do not enter data on cases with late syphilis and clinicians might, as explained in limitations, not report them. Thus we did not decide to include the information on coverage under the Methods.

11. Page 12, First paragraph: “Several cases reported being infected in Russia or Pakistan…”. How many cases were infected in Pakistan?. This figure doesn’t appear in the tables.

Response: The proportion of cases, infected in Pakistan, is stated in the Results under “Men, infected heterosexually”, however the paragraph about Pakistan was now removed from Discussion due to a suggestion by another reviewer.

12. A total of 30% of syphilis cases in women had been diagnosed by contact tracing versus only 7.9% and 8.3% respectively in heterosexual and homosexual men. What do the authors think about these differences?

Response: We have emphasized this now in the first paragraph of discussion, as well as in the recommendations of another paragraph in the discussion (marked green).

13. Abstract:
- Background: Stratification variables should be presented in the methods section
- Methods: Some information about the analysis should be presented
- Results:
In the sentence “The proportion of MSM increased from 0 (1992-1994) to 88% (2007)”, why data of the last year (2008) are not included?
I suggest replacing “The majority obtained syphilis…” with “The majority was infected by a casual partner”

Some information about congenital syphilis should be provided in the results section (congenital syphilis is mentioned Methods but afterwards no data appears in the Results section, which is a bit confusing)

Response: Suggested changes were made. Since only descriptive results were provided in the abstract, we find it unnecessary to provide more detailed analysis description in the methods of the abstract.

14. Results:
Page 6, paragraph 2:
Consider removing “observed” in the sentence “The incidence rate in the observed study period…”

Page 7, line 15:
Consider replacing “During our study period” with “During the study period”

3. Table 1:
Please present median and percentiles for quantitative variables
What does “Indications for testing: Own request” mean?. Do patients seek testing without having symptoms?

4. Figure 2:
It is difficult to distinguish between lines “other STI” and “no reported STI”

Response: Some of the above suggestions were made. For age, we have already given the median and the categories (agegroups) which makes it easy to see the distribution. For duration of symptoms we now give the median and interquartile range.

Patients may seek testing without having symptoms if they are worried after having risky sex. The answer “own request” is one of the answers in the reporting scheme. The term is not explained in detail in the scheme. We have now chosen different colours in Figure 2 to enhance the contrast.

15. Discretionary Revisions:
I would suggest re-ordering the discussion. Sometimes it is difficult to read because the issues are mixed (5th paragraph is about MSM, 6th about heterosexual, 8th about MSM…..)

Response: Discussion has been structured according to following structure: 1 summary of the main findings, 2 strengths, 3 limitations, 4 consistency with other studies, 5 suggestions what the study results mean, 6 ideas for practice and further research, 7 conclusions. According to this structure, it may happen that MSM appear in several separate paragraphs. Upon suggestion of another reviewer, several paragraphs were removed, which we believe has now improved the structure.