Author’s response to reviews

Title: Trends in HIV infection surveillance data among men who have sex with men in Norway, 1995-2011

Authors:

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Author’s response to reviews: see over
Dear Editors,

The authors have now jointly addressed the concerns and questions brought up by three reviewers. You will find our answers below. We are very grateful for the thorough reviews received and found the comments helpful.

We experienced that this article has been in review for a longer period of time and we evaluated adding new data that has become available since – years 2010 and 2011, see changed title above. We have taken the liberty to include those in order to increase the timeliness of the manuscript. We believe most recent data are more interesting to other researchers in the field. Including these two years has not affected our major conclusions.

We hope that our manuscript is now sufficiently improved to be accepted for publication.

We look forward to hearing from you,

Irena Jakopanec, MD
Authors response to the first reviewer

Reviewer: Asuncion Diaz

Major Compulsory Revisions:

1. Methods:
   - Page 6, 2nd paragraph:
     I would suggest moving the sentence “At NIPH, a date of infection is individually estimated from laboratory results, previous negative tests and patient’s information” before the second paragraph in page 7 (“When presenting the cases by the year in which they were most likely infected…).

     The sentence has been moved as you requested.

   - Page 7, 2nd paragraph:
     - What is the difference between “possible” and “probable” time of infection?. In both categories time of infection is less than 3 years. Please, provide criteria to classify cases as “possible”.

     The definition has been further clarified in the manuscript. Both possible and probable cases have been diagnosed within 3 years after infection, but probable cases fulfilled additional criteria, as described. We have now merged “possible” category with “uncertain” years of infection, to simplify this information.

     - More details should be given on how the date of infection is calculated when a past HIV-negative test is available. Is the date of infection the midpoint between the date of diagnosis and the date of past negative test?.

     Yes. The information has been added.

     - “The past negative HIV test” is the same as “the last negative HIV test”?.

     The word “past” was removed and additional clarification that this is most recent negative HIV test was added in the Methods section.

2. Results:
   - Page 7, 1st paragraph:
     - Please present median age with the 25th and 75th percentiles

     We added this information, though age distribution is also represented in age groups frequencies in Table 1.

     - What does “men on temporary visit” mean?

     It means men, who visit Norway temporarily and do not plan to stay – tourists, seasonal workers, students etc. The sentence has been slightly adjusted.

   - Page 8, 6th paragraph:
     “We observed a significant increase among syphilis co-infected MSM (p for trend=0.001) …”. Please, provide some figures and percentages
The manuscript text has been amended to reflect more details about co-infections; however the numbers are small and vary from year to year. It is thus difficult to describe these changes in great detail.

3. Discussion:
• Page 11, 3th paragraph:
I suggest to change the sentence “Similar to our findings, 11% of HIV positive MSM had an STI co-infection in Belgium [9] and 15.4% in Amsterdam STI clinic [11], but as much as 31% in Spain in the period 2003-2007 [13]” for the following: “Similar to our findings, 11% of HIV positive MSM had an STI co-infection in Belgium [9] and 15.4% in Amsterdam STI clinic [11], but as much as 31% in Spain in the period 2003-2007; nevertheless the Spanish data are not derived from a universal surveillance system but from a network of STI clinics[13]”

Adjustments have been made to reflect the origin of the data.

• Page 13, 1st paragraph:
Could you, please, clarify the meaning of the sentence “We did not identify a large discrepancy between the year of infection and the year of diagnosis…”.

The sentence has been deleted.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. Methods:
• Page 6, 3th and 4th paragraph:
I suggest re-order this section. My suggestion would be to put the 3th and 4th paragraph (data analysis) at the end of the methods section.

The paragraphs have been moved.

2. Reference List:
There is an erratum in the reference number 3.

Thank you, the mistake has now been corrected.

3. Table.
I suggest to include a column with the description of cases diagnosed from 1995-2003.

This column was previously not included because the information can be deducted from a column with all cases (“total sample”) minus cases diagnosed from 2004-2009, however we have now added it.

4. Figures
- To be consistent with the rest of the manuscript, I would suggest writing “men who have sex with men” instead of “cases with homosexually acquired HIV infection” in the figures legends.
The titles were changed as you suggested.

Discretionary Revisions:

1. Background:
Could you provide some information about HIV infection in Norway by mechanism of transmission?. This could help the reader to understand the importance of MSM in the HIV epidemic in Norway.

We have now provided some additional background on cases, infected with sexual transmission, emphasising the vulnerability of MSM (second paragraph). We have not, however, provided the details of less represented transmission groups, as this is not the aim of our article. The reader will be able to find further resources on the remaining transmission groups in Norway from our references.
Authors response to the second reviewer

Reviewer: Alison E. Brown

Major compulsory revisions:
1) The authors categorise whether patients were infected by a casual or a steady partner. How is this information ascertained? Many men will have both casual and steady partners. Patients’ assumptions about their potential source of infection may not be valid.

The clinicians perform contact tracing and report the data on partners. They are responsible to evaluate the likelihood of transmission among partners, based on patient history. Limitations of behaviour data, obtained by clinicians, have been added to the discussion in our manuscript; however, these exist in any STI study, where phylogenetical data are not available.

2) The attempt to explore trends in transmission is commendable, but too much is drawn from categorisation of patients in relation to length of time between diagnosis and infection. It is not clear how “uncertain” or “possible” time of infection was defined. The uncertainty of the method for allocating time since is infection is vast…there needs to be much more discussion of the caveats surrounding this in the discussion. Specifically, the translation of this method to conclude “there were many infections in 2003 is simultaneously vague (how many?) and too specific (how can you be certain this is 2003?). It would be useful to have a table to breakdown patients in each category which also quantifies the possible variation.

We have now clarified further our definition of uncertain and probable times of infection in the Methods. We merged “possible” category with “uncertain” years of infection, to simplify this information.

We believe quantification a table instead of the figure may give a false reassurance. We created the Figure 4 in order to illustrate the most likely years of infection. In the absence of any other possibilities to evaluate year of infection, we believe this approach is of value. We summarized the numbers in each category in the manuscript text.

The caveats of the above methods were emphasized further in the discussion.

We amended our conclusion for the Figure 4. This figure also illustrates the degree of certainty for information on years of infection.

3) I would have liked to have seen more shown in terms of distribution of age at diagnosis over time. The fact the median age at diagnosis remains constant over time is indicative of steady transmission - more could be made of this

A figure with 25, median and 75 percentile of age of the cases was added and more effort was made to interpret these results.

4) The thinking behind comparing trends before and after 2003 due to an
outbreak in 2003 is not clear. It perhaps would have been better to group into three periods, with 2002-2003 as mid period.

The thinking is described in the last paragraph of the background, but we have now emphasized our idea. We wanted to see if there are any differences in cases diagnosed after 2003 (after an increase in diagnosed cases) compared to earlier years. Grouping in three periods is not of our interest. We think grouping 2002 and 2003 together in a single mid period is not interesting, as there seem to be some change between exactly these two years, suggested by doubling in number of cases and simultaneous fall in median age.

More needs to be described about this outbreak...outbreaks of HIV are notoriously difficult to define...was this based upon phylogenetics or just an increase in the number of new HIV diagnoses?

Norwegian HIV surveillance system, where the data were taken from, unfortunately does not collect phylogenetical data. Linkage would not be possible due to existing privacy laws. We agree we should avoid using the word outbreak, so it was removed from this context.

5) The authors suggest that the data show that half of MSM were diagnosed “early” – I may argue otherwise given this definition is based upon seroconversion illness or asymptomatics infection...is the increase in asymptomatic reporting due to improved reporting

The sentence at the beginning of discussion has been amended. We added a clarification in paragraph 3 in the Discussion. Limitations of this approach were further stressed in the Discussion. We have further clarified the uncertainty of information on year of infection in the Methods and presented it in the results. We do not think there were any changes in the reporting, given the system in Norway, described in the Methods.

6) The table could be better thought out...a frequency table may reveal more than that showing linear regression for all available variables.

Our previous table displayed frequencies in total sample and frequencies in those, diagnosed after 2002 (so the information on infected before 2003 had to be deducted from these two columns). The table has now been changed and we have now added a column with frequencies for those, diagnosed in 1995-2002. We hope this adds to clarity of the information presented.

7) the figures place too much emphasis on time since infection which is subject to the uncertainty above

We hope that it is now clearer that we wanted to address the uncertainty of estimated time since infection by creating a figure, where the likelihood of estimate being correct was reflected (Figure 5). The limitations of this approach are now further emphasized in the discussion.

Minor compulsory revisions
1) The written English could be improved

We agree with your comment and the manuscript has now been revised by a native speaker.

2) The title reads as through it is trends in SURVEILLANCE that are being monitored, rather than trends in HIV infection

Thank you for this remark, indeed, the title needed to be changed.

3) The discussion compares increases in new diagnoses across Europe, some papers cited are out of date (e.g. UK)

We have updated citations.
Authors response to the third reviewer

Reviewer: Brian Rice

Discretionary Revisions

1. In the Methods a better description of the systems used would be helpful.

We are uncertain which part is not clear, but have made changes throughout the Methods, as you and other reviewers suggested.

2. Page 10 1st paragraph: should the limitation on undiagnosed HIV be turned into a recommendation for monitoring this?

Indeed. This recommendation has been made in the previous version on page 13, paragraph 2 and we have now emphasized it further by putting it in the final conclusion.

3. Page 10 1st paragraph: “The increase in cases was predominately due to the recently infected” – this is very definitive and until the reader better understands what is meant by incidence is hard to assess.

We agree. The text has been amended.

4. Page 11 2nd and 3rd paragraphs – some of the references are old – could the references please be updated.

We have updated citations.

5. Page 12 paragraph 2 – do we think men from the USA and Europe fall into the category of being from cultures where homosexuality is not accessible?

Hopefully not, so we now changed the paragraph to make it clearer.

6. In relation to final sentence of paragraph 2 on page 12 could it not also be a lack of self-perceived risk or due to acquisition of HIV post arrival, or screening not being appropriate?

We have expanded this into a paragraph, adding corresponding information on heterosexual group. Screening for immigrants is the same for MSM and heterosexuals; hence the results should be similar.

7. Page 13 1st sentence – as there was a discrepancy do the authors mean there was no change in this discrepancy over time?

Yes. The sentence has been changed.

8. Page 13 1st sentence – the term “rather” should be avoided and replaced with a more specific term.

This word has not been used in the revised manuscript.
Minor Essential Revisions

1. Throughout the document the authors should ensure correct sentence and paragraph (i.e. refrain from one sentence paragraphs) structure is followed. In particular, the 3 articles in English (a, an and the) should be applied correctly as they are often missing. Examples of where corrections could be made include:
   a. Background 1st sentence page 4 – “IncreaseS in HIV transmission among men who have sex with men have recently…”
   b. Background last sentence page 4 – “…..better insight in to the development of the HIV epidemic…..”
   c. Results 2nd sentence page 8 – “Thirty-two men had previously tested positive abroad, 15 of whom….”
   d. Results page 8 – “Among 98 men with a simultaneous…..” etc
   e. Discussion page 10 – “…HIV positive people who immigrated to Norway…..”

   One sentence paragraphs have been avoided as much as possible. The manuscript has been reviewed by a native speaker to correct typical mistakes you describe. We have of course taken into account your corrections as well.

2. Ensure references are provided where necessary. For example, Methods 1st sentence page 5 – a reference should follow this sentence.

   Legislation reference was added.

3. Could the authors standardise their use of MSM or homosexual as the first includes bi-sexual men whereas the latter does not.

   We now aimed to use MSM throughout the manuscript.

4. Paragraph 3 page 4: Not clear how the authors conclude that HIV incidence is largely influenced by testing uptake – does not surveillance data monitor the incidence of diagnoses rather than transmission? This sentence needs to be clarified, supported, or removed.

   Thank you, the sentence has been clarified.

5. Paragraph 3 page 4: Second sentence should be included in the discussion as a limitation of the analyses.

   The paragraph has been moved to Discussion.

6. Page 7: The authors describe an algorithm for assigning cases into three categories; it would be useful to understand data completion / numerical assignment.

   Definition of categories is provided in the Methods, while numerical results are provided in the Results section. Note that information on evaluation of time of infection is not only subject to data completion, but also data availability. The NIPH makes efforts for each individual report to have highest data completion possible – see Discussion part.
The three categories have been further clarified in the Methods, as suggested by other reviewers.

7. In the Methods could it be made clearer as to what is meant by “Only one co-existing STI is recorded”? Table 1 refers to “Any” “STI co-infection” – what is meant by this if only one STI is recorded?

Information on co-existing STI is put into a single variable, so a single co-existing infection would be cherry-picked at NIPH, if there would be multiple reported (which is very rare) on the form. Picking among which infections to include is done in a “hierarchical” way (syphilis being always recorded, if reported) and put into a single variable rather than several parallel variables.

The rest of the information is currently (sometimes?) entered in the free text field. We have made attempts to retrieve this information from the free text field, but this revealed that multiple co-existing STI were quite rare (less than 5 cases with multiple co-existing STI were found) and this was not considered interesting for the article.

Thus, the proportion of those with any co-existing STI (regardless of which one specifically), will be a correct estimate and has thus been entered into the Table as a variable “any” (co-existing STI) reported.

The text in the Methods has been amended to provide more clarity on this.

8. In the results, please be clear of time periods referred to throughout; an example is where median age at diagnosis is referred to – when?

We have amended the manuscript accordingly.

9. In the results what is meant by “AIDS”? This should be clearly defined and referred at the very least as “an AIDS defining illness” – being specific about which illnesses would be preferable.

Detailed definition of AIDS and specification of illnesses are beyond the scope of this manuscript. The authors believe AIDS is a widely recognised clinical term, but its definition was now clarified with a reference to European AIDS definition in the Methods section.

The clinician will have to report AIDS on a separate form, so both HIV and AIDS forms would be received for these cases at NIPH. Thus, we can be sure this is AIDS, not an AIDS defining illness.

10. When it is stated in the last paragraph of page 8 that there have been increases it would be useful to understand from what and to what there has been an increase as no table or graph is referenced.

We now tried to describe the trends as best as we could, given the numbers are small and vary greatly from year to year. The table could be provided, if desired, but would come with limitations in the way co-infections are registered at NIPH, as described in the Methods.
11. Page 9 last paragraph – it is not usual practise to end the results with a sentence on data completion – either remove to the beginning of the results or preferably to methods (and include this for other variables).

As explained above, this is not data completion, but also data availability (and degree of certainty of the time of infection estimates). We think this belongs to the Results section.

12. Table 1 refers to GP testing but this does not appear to be referred to in the results section – please ensure that variables included in tables and graphs are at least raised in the text (obviously the figures can be referenced to the tables or graphs).

We have changed the manuscript accordingly.

13. The discussion focuses on system attributes rather than the findings and policy implications of the results – please address.

This is a very good proposal and we have addressed this as much as possible.


This has been amended.

15. Page 13 1st paragraph – the authors should make clearer their thinking around the “rapid and recent HIV spread” and “undiagnosed cases” and possibly, if relevant, how late diagnosis would fit.

We do not have data on CD4+ levels, but have included AIDS trends. The vague descriptions have been removed.

16. Page 13 2nd paragraph – are the references in the correct order? If not, please amend.

The references were in the correct order.

17. In the conclusions it is not clear how “burden” has been shown – please make clear what is meant by burden.

The sentence has been slightly rephrased.

18. The key conclusion that PEP should be on the PH agenda comes out of the blue – if this is the key conclusion then it would be good to also discuss PEP further in the introduction and discussion.

We agree and have removed the PrEP from final conclusion.

Major Compulsory Revisions
1. Page 6 and page 7: Could further details please be provided as to how “presumed time and place of infection” is arrived at as this is crucial to the analyses (particularly given that in the results the authors refer to “who were infected in....” rather than “who were probably infected in...”)? Knowing time of infection is hard to ascertain so it is of interest as to how cases are presented by the year of their infection and how “exact date of infection” can be known. It is essential that it is clear to the reader what is meant by “incidence” and by “time and place of infection”.

Exact date of infection would be known if a clinician has found a single risky exposure in the past, where a man is very likely to have been infected and the date is known. We believe we have now presented the data more properly, to give the idea on reliability of information, used for presumed time of infection estimates.

2. Page 9 first paragraph – I would suggest restructuring this whole paragraph as it is not clear; be clear as to whom certain groups are being compared; refrain from using vague terms such as “They were more likely to have lacking information...” as it is not clear as to whom you are referring, to whom you are comparing and to what extent there was a difference (please insert figures); when stating “After adjustment for other factors....” please be clear as to what these factors are in the text or clearly reference the relevant table or graph.

We have amended the paragraph and hope it is now clearer.

3. In results it is usual practice to make clear to the reader what was found to be significant in univariate analyses, what remained significant in multivariate analyses, and to provide specific figures and p values throughout. Please amend accordingly.

In results, confidence intervals rather than p values are provided, which we believe are sufficient. Unlike confidence intervals, the p value is set at arbitrary value (0.05) and does not indicate the potential direction of association. Many papers on this debate exist, here is an example, reflecting our opinion:


Furthermore, what was found significant is described in the text of the manuscript and “borderline significant” p values were also mentioned there.

4. Page 13 3rd paragraph – the limitation described is a very important one and should be described in better detail (and quantified if possible) and moved closer to the beginning of the discussion.

Good suggestion, we have acted accordingly.

Quality of written English: Needs some language corrections before being Published
We agree with your comment and the manuscript has now been revised by a native speaker.