Author's response to reviews

Title: Completeness of Registration of HIV and Hepatitis B and C Coinfection in The Danish National Hospital Registry, 1995-2004

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Author's response to reviews:

To the Editor in Chief, BMC Medical Research Methodology.

Thank you for having reviewed our paper: “Completeness of Registration of HIV and Hepatitis B and C Coinfection in The Danish National Hospital Registry, 1995-2004”, which presents findings from the Danish HIV Cohort Study.

Below we have inserted our answers in to the questions raised by the reviewers. Further a revised manuscript is forwarded. We hope that our answers are sufficient to have the paper published in your journal.

Sincerely

The authors

Reviewer's report

Title: Completeness of Registration of HIV and Hepatitis B and C Coinfection in The Danish National Hospital Registry, 1995-2004

Version: 1 Date: 8 October 2007

Reviewer: David B. Preen

The proposed work initially aims to examine the completeness and accuracy of recording of HIV infection in the Danish National Hospital Registry (DNHR) from 1995-2004, by comparison with data obtained for the Danish HIV Cohort Study. Additionally, the study proposes to identify the level of recording of hepatitis B and C for people with HIV in the DNHR, as well as establish temporal
associations with recoding of such information.
The study focuses on an interesting methodological area which, will likely be of interest to those relying on similar data sources for research purposes. Further, given the continued rapid developments in information technology and willingness of researchers to utilise such data, the results perhaps have implications for future investigations.
The manuscript was generally well structured. However, while the primary aspects of the planned research were well presented, some methodological issues possibly exist that require clarification or further consideration.
Furthermore, the manuscript was a little too brief in many instances. As such, there were some sections of the paper (specifically the Methods and Discussion) which could have benefited from the provision of a greater level of detail or additional commentary. Specific comments relating to the primary areas of concern, categorised according to the journal’s revision criteria, are as follows:

Major compulsory revisions
Abstract: While generally well-structured, the abstract is somewhat short/brief. Specifically, a large portion of the methodology and results (eg, Cox regression, hazard ratios etc) are not mentioned.
Answer: Cox regression has now been mentioned in the method section of the abstract. Further the predictive values of CD4 count, viral load and being diagnosed after 1. January 2000 have been mentioned.

Further it has now been stated in the manuscript: Thirty (23%) HIV patients registered with chronic HBV (n=129) in DHCS and 126 (48%) of HIV patients with HCV (n=264) in DHCS were registered with these diagnoses in the DNHR. Further 17 and 8 patients were registered with HBV and HCV respectively in DNHR, but not in DHCS. The positive predictive value of being registered with HBV and HCV in DHCS was thereby estimated to 0.88 and 0.97 and in DNHR 0.32 and 0.54.

Further, while sensitivity results are displayed, this analysis is not mentioned in the Methods section. This is similar for the temporal associations reported in the results but not referred to in the methods section of the abstract. In addition, the 1½ line conclusion requires more detail.
The conclusion part of the paper has been generalized: The study demonstrates that secondary data from national hospital databases may be reliable for identification of patients diagnosed with HIV infection. However, the predictive value of co-morbidity data may be low.

What concerns the sensitivity analysis it is mentioned in methods that:
In a sensitivity analysis we expanded these groups to include nonspecific viral hepatitis as follows:

Chronic Hepatitis B and nonspecific chronic viral hepatitis: B18.0, B18.1, B18.8, B18.9
Chronic Hepatitis C and nonspecific chronic viral hepatitis: B18.2, B18.8, B18.9

We find this explanation sufficient.

Methods ¿ One aspect that was not clear from the paper is whether the DNHR contains only primary admitting diagnosis/procedure information or whether it also includes secondary diagnoses and co-morbidities (as with many other hospital discharge registries). This requires clarification as it has major implications for the study. If only primary diagnosis is recorded, this would likely be the major underlying explanation for the low sensitivity observed in this data set for hepatitis B and C by the study. Further, if comorbidity information is collected, how many conditions are coded in the registry data? Also, if coded is it likely that only conditions relevant (or perhaps similar) to the principal diagnosis are recorded in the medical notes? Information on these aspects of the DNHR data is essential for the study methodology. In addition, a greater level of commentary is required on this issue in the Discussion section.

Answer: It has now been stated in the method section, that: ¿ Primary diagnosis as well as co-morbidities are coded in DNHR. Further this part is now discussed in the discussion section.

Discussion ¿ The Discussion section was too brief and perhaps a little superficial in some places. Few comparisons with previous research findings were included. Further, when comparisons were made few specific details were provided. For instance, with comparison of the current findings to previous work on acute myocardial infarction etc, some specific results from these other studies would have been useful. In addition, given the limitations, and the jurisdictional-specific focus of the current study, some discussion of potential recommendations for further/future research was required.

Answer: The discussion has been extended considerably. However, we do not find, that the results from studies of e.g. myocardial infarction should be repeated in the discussion section of the actual paper.

Minor essential revisions
Methods ¿ While briefly discussed in the Discussion section of the paper, some information on the number and proportion of patients with HIV who do not seek
medical treatment for their condition is warranted. While, I am assuming that it would be a relatively small number, some published precedent or more detailed information regarding this issue would be useful in the Methods section.

Answer: We have now stated in the paper. Further the fact that antiretroviral treatment is in Denmark restricted to these eight clinics ensures that very few patients diagnosed with HIV remain unrecognised by DHCS.

Given that many readers may not be familiar with the DNHR, a greater level of background information on this data source should be included in the Methodology. Specifically, what information is collected (eg, only primary diagnosis or also comorbidities)? Also, is the Registry routinely audited, or has any validation work ever been carried out indicating the accuracy and completeness of the data for other diagnoses?

Answer: it is now stated, that primary diagnosis as well as co-morbidities are registered.

While acknowledged by the authors, the major limitation for the study was that they were not able to compute predictive value of a HIV diagnosis in the DNHR since [they] did not have permission from the Danish Data Protection Agency to identify HIV cases recorded only in the DNHR. In addition to restricting analysis of positive and negative predictive value, this limitation also restricts evaluation of specificity of the data maintained within the DNHR. Consequently, it represents a major issue for the study and considerably decreases the quantity and quality of the findings that could be generated. However, given the implications of this limitation, relatively little discussion is devoted to this issue in the Discussion section of the manuscript and further commentary is warranted.

Answer: We have added a paragraph about the implications of not being able to analyse predictive values.

A comparison between two data sources alone does not provide the opportunity to estimate specificity, but it can be assumed that specificity will be close to one if the background population is large and the disease rare (ref:Sorensen et al. Int J Epidemiol. 1996 Apr;25(2):435-42). Thus we find that it is an acceptable limitation that we can not calculate specificity.

From the description presented, I am assuming that the study is comparing DNHR data to that recorded in the DHCS for only those HIV patients actually admitted to hospital, or attending a captured outpatient service, during the study period. However, this is not clearly stated in the manuscript. Some comment to this effect is warranted, as otherwise it could be perceived that comparisons were
made for all patients captured in the DHCS regardless of whether they were `hospitalised`. This would be a completely different research question, as it would be expected that there would be an under-ascertainment simply due to those patients not requiring secondary health care services for their condition.

Answer: It has now been clarified that treatment of HIV patients also what concerns antiretroviral treatment is restricted to the eight centers participating in DHCS. Further this aspect has been expanded on in the discussion section.

In the first paragraph of the Methods section, age and race are not mentioned as terms to be included in the Cox regression analysis. However, these factors are then presented in the text of the Results section.

Answer: We do not exactly understand this question. The first paragraph in the Method section is `Setting`, which of course do not include covariates for cox regression. In the statistical section it is stated, that age and gender is included in the cox regression.

Results: Throughout the Results and Discussion Sections (as well as in Table 2) comments are made relating to the `risk` or `relative risk` of various outcomes.

However, these estimations are derived from Cox regression analyses which provide proportional hazard estimates (ie, hazard ratios). While they may approximate relative risks, they are technically two different measures.

Consequently, these instances in the text should be reworded to remove mention of relative risk.

Answer: It is stated in the paper, that: `Cox regression analysis was used to estimate hazard ratios (HR) as a measure of the relative risk of being registered with an HIV diagnosis in DNHR.` Rephrasing `risk` to hazard ratios would in our opinion make the text unnecessarily complicated to the clinical reader of the journal. We are sure, that the experienced epidemiologists, who are aware of the technical difference between hazard ratios and relative risk and the background for the approximation, will be able to understand this as well.

For the comment that `of note, some patients with [a] HBV or HCV diagnosis recorded in the DNHR did not have a corresponding record in [the] DHCS`, some indication of the number or proportion of patients who fell into such a category would be useful here.

Answer: these numbers are stated in table 3, to which the text now refer.

Further, were sufficient data noted to allow at least a
quasi-analysis of specificity or predictive value for these variables? If so, then such an inclusion would strengthen the article. If not, perhaps a brief statement to this affect would be a worthwhile addition.

Answer: It has now been stated in the text:

Of note, 17 patients were registered with HBV (ICD10: B18.0 and B18.1) and 8 with HCV (ICD10: B18.2) in DNHR who did not have a corresponding record in DHCS (table 3). Assuming that the correct numbers of HBV and HCV is 129 + 17 = 146 and 264+ 8 = 272, the positive predictive value of being registered with HBV and HCV in DHCS was 0.88 and 0.97 and in DNHR 0.32 and 0.54 respectively.

Discretionary revisions

Title  The title is perhaps a little misleading as to the true focus of the study. As it currently stands, the title does not make it clear that the study will investigate hepatitis C and B in only those patients previously identified with HIV. I would suggest altering the title to improve clarity of your study focus and target population.

Background  This section, while perhaps a little brief, was generally well-structured and created a clear rationale for the study question to be investigated.

Methods  It would be worthwhile providing some additional brief description for the other variables contained in the DHCS. For example, was there information available on demographic, socioeconomic, clinical etc data?

Answer. It has now been stated that: The date of HIV diagnosis, dates of AIDS-defining diseases and HBV and HCV status, are registered for each patient in DHCS as well as AIDS defining events, antiretroviral treatment, HIV-RNA, CD4 counts etc.

Results  Table 3 is mentioned in the text of the Results section prior to Table 2. Tables should be numbered in the order in which they appear in the text.

Answer: has been changed.

Note that age, CD4 count and log viral load results presented in Table 1, do not really fit under the total number of patients column heading. In addition, units should be included for age, CD4 count and log viral load results.

Answer: The heading is Characteristics of HIV patients registered in the Danish HIV Cohort Study and not total number of patients. Unit for age, cd4 count and viral load has been included.
Discussion

While I agree that, given the nature of HIV infection, some of the study results may be able to be generalised to other countries with similarly organised health care systems, more detail on the ability to extrapolate findings to other specific countries (e.g., other European nations, the US, Canada, Australia etc) would be useful.

Also, given the ever emerging capacity to analyse large administrative health data sets, some commentary on the implications of the use of data from such registries is warranted. In addition, some discussion of previous researchers who have already attempted to investigate hepatitis C or B from such hospital registries would be an important inclusion for the Discussion section, as it is likely that such researchers have made erroneous conclusions from their research.

In-text references

Answer: we have added a paragraph (on top of page 15) where we discuss the potential bias associated with lack of completeness of hepatitis C registration.

There are a number of instances where factual statements are made without supporting citations to back up the assertions. Examples of such instances where supporting references are required as follows:

Introduction, paragraph 1, sentence 2
Introduction, paragraph 2, sentence 3

Answer: That HIV is world wide spread, has high impact on morbidity and mortality etc. we find is well know and need no reference. A reference is inserted for sentence 3.

Recommendation:

Based on the review of the article, it is my opinion that the article is of sufficient quality to warranted publication, subject to the authors attending to the above-mentioned issues.

Verdict: Accept after minor essential revisions

Level of interest

As indicated in the above review comments, this paper while methodologically focussed, of limited clinical scope and jurisdiction specific, would still likely be of interest to investigators relying on similar data sources for research purposes.

Further, given the continued willingness of researchers to utilise such administrative data sources, the results perhaps have implications for future researchers.
Verdict ¿An article whose findings are important to those with closely related research interests¿

Quality of written English

One more minor issue was that a reasonable number of grammatical errors or formatting inconsistencies were noted throughout the manuscript. Examples of such grammatical and formatting issues are outlined below.

¿ Title ¿ Should ¿The Danish ¿¿ be capitalised?
Answer: has been changed.

¿ Background section ¿ On the first line of text, the abbreviations AIDS and HIV are not defined, likely as they were previously defined in the abstract. However, in contrast abbreviations such as HBV, HCV, DNHR and DHCS are re-defined in the introduction. Further, some abbreviated terms are additionally defined on multiple occasions throughout the text (eg, DNHS and DHCS defined in abstract, introduction and methods). It is recommended that the formatting structure be kept consistent for all such terms, as per the journal¿s formatting guidelines
Answer: has been changed.

¿ Minor point, but in the first paragraph of the Results section two percentages are rounded to the nearest whole number (ie, 93% and 96%), while another is expressed more precisely (ie, 98.7%). I would suggest expressing all percentages consistently, according to the journal¿s formatting guidelines.
Answer: has been changed.

¿ Discussion ¿ Reference is commonly made to ¿an HIV treatment centre¿, whereas this should be rewritten as `a HIV treatment centre¿. Similar for ¿an HBV or an HCV diagnosis¿, ¿an HIV hospital treatment centre¿ etc. Also, it is grammatically correct to refer to the DNHR or the DHCS.
Answer: according tour knowledge it is ¿an¿ before and ¿H¿, when it is pronounced H-I-V etc?

¿ Spelling/grammatical error (ie, ¿twese¿) on third line of last paragraph in the Results section.
Answer: sorry, has been changed.

Also, in the same paragraph, is this meant to be p<0.05 and p<0.01, as p=0.05 is not technically statistically significant?
Answer: it is p=0.053, which is rounded to 0.05, and p=0.013 which is 0.01 when
rounded.

In table 2, the lower bound confidence interval of 0.863 should be rounded to two decimal places to be consistent with the rest of the table. Answer: has been changed.

Also for Table 2, a closed-bracket is required for the confidence interval under the crude analysis heading for Centre 3. Answer: has been changed.

Verdict: Needs some (minor) language corrections before being published.

Declaration of competing interests:
I declare that I have no conflicts of interest or competing interests (financial or non-financial) with either the submitted paper or contributing authors.

Title: Completeness of Registration of HIV and Hepatitis B and C Coinfection in The Danish National Hospital Registry, 1995-2004

Version: 1 Date: 26 September 2007
Reviewer: Morten Frisch
Reviewer's report:
General
This paper aims to evaluate the completeness of registration of HIV infections in the Danish National Hospital Registry (DNHR) for the period 1995-2004, using data for 2,033 HIV patients from the Danish HIV Cohort Study (DHCS), which is considered to be highly accurate and virtually complete and covering all Danish HIV Clinics, as the golden standard. Additionally, completeness of registration in DNHR of coinfections with Hepatitis B (HBV) and Hepatitis C (HCV) was evaluated, again using DHCS data as reference. Overall, the study documents virtually 100% completeness of registration in the DNHR of clinically established HIV infections recorded in the DHCS database. Less than complete registration in DNHR takes place of coinfection with HBV and HCV. With appropriate extensions and modifications I believe the paper will become a valuable piece of background information for epidemiologists and infectious disease specialists with a research interest in HIV.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
While it is reassuring that almost 100% of established HIV diagnoses in the
DHCS database can be retrieved in the DNHR, the study is currently unable to judge the specificity of HIV diagnoses recorded in the DNHR. In the 'Statistical analysis' section, the authors state that they did not have the necessary permission to identify HIV cases recorded only in the DNHR, which is required for such evaluation of the specificity. For epidemiologists and clinical researchers who want to use DNHR data to identify HIV patients, the specificity of HIV diagnoses in the DNHR is of central interest. Put simple, we learn from this study that virtually all confirmed HIV diagnoses (obtained in the DHCS database) are also accurately registered in the DNHR data, but the study does not tell what proportion of all recorded HIV diagnoses in the DNHR actually represent clinically and laboratory-confirmed HIV infections. It would be immensely useful if the authors extended their analysis so as to provide such information about specificity and positive predictive value (PPV) of HIV diagnoses obtained in the DNHR. Presumably, it will require only a minor administrative effort to obtain permission from the Danish Data Protection Agency and the National Board of Health to get access to all DNHR information about HIV, HBV and HCV infections in the DNHR. This would not only make an assessment of the specificity and PPV of DNHR-based HIV diagnoses possible; it would simultaneously make an evaluation of the completeness of HBV and HCV coinfections in the DHCS database possible.

Answer: As stated this is at present time not possible. Being HIV infected is still stigmatizing in Denmark. Further Danish law does not allow a complete register of HIV infected patients. In case we did perform a complete merger of DNHR and DHCS we would come very close to this national HIV-register. We are doing a lot of research in HIV in DHCS even in collaboration with the HIV patient organizations in Denmark. We do not want to challenge Danish law, ethics and patient organization just to gain this little more information. Some HIV patients want to go unrecognised at least for the period until they need antiretroviral treatment. And we find this should still be possible. So yes, a complete registration would be one very little step I epidemiology but a huge step in law and ethics. Further the aim of the study was to establish to what extend HIV was registered in DNHR, not if DHCS registered all HIV patients and DHCS does not include all Danish HIV patients, but all HIV patients seen in centers treating HIV patients (and therefore we presume that it includes ALMOST all patients).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
The title of Table 3 is somewhat misleading, as the table does not present
numbers of patients diagnosed with HIV, HBV and HCV in the DHCS and DNHR. Rather, this table presents data on HIV, HBV and HCV diagnoses among the 2033 HIV patients identified in DHCS. Currently, the title could be rephrased to something like: "Registrations of HIV, chronic Hepatitis B, and chronic Hepatitis C infections in the Danish National Hospital Registry (DNHR) for 2033 HIV patients identified in the Danish HIV Cohort Study (DHCS) ", but I'd much rather see an extension of the table, in which the above suggested new DHCS-independent DNHR data on HIV, HBV and HCV infections for the study period are also included.

Answer. Has been changed according to the suggestion by the reviewer,

Additionally, it is not entirely clear how the authors calculated percentages for HBV and HCV in Table 3. In the title, but not in the Abstract or in the Results section, the authors state that the percentages relate to the sum of diagnoses in the two registries (DNHR and DHCS). However, the percentages shown in the body of the table relate only to the number of diagnoses in DHCS. E.g. the 30 DHCS-based HBV diagnoses that were retrieved in the DNHR database represent 23% of the total of 30+99=129 HPV diagnoses in the DHCS data-base, not to the 146 HPV diagnoses that were found in the two databases combined.

Answer: The reviewer is completely correct. This has now been changed.

From the Results section, second paragraph about "Predictors of early registration" and the accompanying Table 2 it is not clear what the term "early" means. To me, it seems that the entire Table 2 deals with determinants of registration overall, and not specifically with determinants of "early" registration. This is somewhat confusing, as the next section in the results section deals with mortality in relation to early (<3 months) vs. later registration of HIV in the DNHR.

Answer: we have rephrased this.

The final sentence in the Results section about changing trends in hepatitis registration among HIV patients over calendar time is quite hard to understand. Please rephrase. If I get it right, I suggest the sentence rephrased to something like: "The registration in DNHR of chronic hepatitis infections for the 2033 HIV patients in DHCS increased over time, with 26% and 42% of all DHCS-established HBV and HCV coinfections, respectively, registered in the DNHR for the 1995-1999 period, versus 41% (p=0.05) and 57% (p=0.01),
respectively, of such hepatitis coinfections registered in the DNHR for the 2000-2004 period.

Answer: Has been changed according to the reviewers suggestions.

The rationale for analyzing and presenting the analysis of mortality in relation to early vs late DNHR registration has not been described in any detail. Please inform the reader why this analysis requires attention. Maybe, given the non-significant findings, Figure 2 can be dropped.

Answer: The rationale for this analysis was to examine whether mortality and probability of being registered in DNHR is associated. The analyses did not show such an association. We have added a sentence about this in the discussion section (page 14).

Discretionary Revisions (which the author can choose to ignore)

Page numbers would be helpful.

I suggest that Tables 2 and 3 be interchanged, because results in Table 3 are presented before results in Table 2.

Answer. Has been done.

First page of Methods section:

* Number 100,000 should be 100,000

Answer: has been changed.

* Study subjects: We learn that patients are identified from the lists of HIV patients in the eight centres, as well as from databases of patients tested for HIV RNA and/or CD4 cell counts. Please give slightly more information about how these latter HIV RNA and CD4 cell count databases differ from the eight centres, and give the reader an idea of what proportion of the 2033 HIV patients that came from these additional sources outside the eight centres.

Answer: these databases are located in the eight centers. So the local data sources on cd4 count and HIV-RNA are only used to ensure, that no patients are treated in the eight centers without being identified by the centers. Has been clarified in the text.

Second page of Methods section:

* Patients were age older than 16. Does this mean 16 years or older or 17 years or older?

Answer: has been clarified in the text.
Second page of Discussion section:
* Line 1: I suggest the word biased be changed to influenced.
Answer: We have changed the sentence to was only influenced slightly by.

* Line 3-4: and patients diagnosed in later years were registered earlier should be changed to and patients diagnosed in later years were more likely to be registered in DNHR. (I believe that this analysis is not about determinants of earlier vs later registration, but of registration vs. no registration in DNHR overall).
Answer: We have now rephrased the sentence according to the suggestion.

* Line 8: all are -> are all
Answer. This have been changed

References:
Check for completeness and typos in references 4, 5, 8, and 9.
Table 1: I suggest that all percentages be presented with 1 decimal, including for Male sex and Other and unknown ethnicity. Additionally, the header Race should be introduced before Caucasian.
Answer: we now present all percentages with one decimal and added the header race before Caucasian.

Table 2: Some HR are presented without an obvious reference category, e.g. Age, CD4 count, Viral load, Diagnosed after 1 January 2000.
Answer: We have added reference categories in table 2 (now table 3)

Figure 2: Consider omitting this figure (see above)
Answer: we have decided not to omit this figure, please refer to our answer above

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report
Title: Completeness of Registration of HIV and Hepatitis B and C Coinfection in The Danish National Hospital Registry, 1995-2004
Version: 1 Date: 14 October 2007
Reviewer: Adrian Levy
Reviewer's report:
General
The authors motivate this study by asserting that "hospital-based discharge registries are used increasingly for longitudinal epidemiological studies of HIV". The authors also include in the results and conclusion the coding of infectious hepatitis. The motivation of the study needs to be made more consonant with the results that are presented.

-------------------------------------------------------------------------------------------------
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The "raison d'être" and the structure of the Danish National Hospital Registry needs to be articulated.
What is the distinction between "computerized hospital database systems" and the Hospital Registry? Patient or treatment registries are structurally distinct from hospital discharge abstracts and the data are typically collected for different ends.
Answer. The description of DNHR has now been extended.

As written, the conclusion of the abstract is a result. Instead the authors should consider giving an interpretation that links back to the reworked motivation of the study.
Answer: the conclusion has been changed, see above.

What is meant by the second sentence of the Introduction, "... making it ideal for epidemiological research"?
Answer: as described: "valid diagnostic tools, well-described risk factors, unambiguous disease outcomes, a high impact on morbidity and mortality, worldwide dissemination, and huge economic consequences commanding the attention of national and international leaders. Epidemiologists like when outcomes, risk factors, observation time and patients at risk are well defined. Hazard ratios and Kaplan-Meier curves are not appropriate statistical measures. The notion of time that is incorporated in the analysis requires some more
elemental thinking.
Answer: we do not agree.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)
What next?: Reject because scientifically unsound
Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests