Author's response to reviews

Title: Seroprevalence of hepatitis C and associated risk factors in urban areas of Antananarivo, Madagascar.

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Author's response to reviews: see over
Reviewer's report - response

Title: Seroprevalence of hepatitis C and associated risk factors in urban areas of Antananarivo, Madagascar.

Version: 1 Date: 3 August 2007

Reviewer: George Strickland

Reviewer's report:

General

This descriptive paper by 13 biomedical scientists in Madagascar reports the prevalence of, and analyzes risk factors for HCV antibodies (anti-HCV) and RNA in a stratified sample of 2,169 subjects in an urban area. Twenty-five (1.2%) subjects met their criteria for being antibody positive and 17 (68%, not the 47.2% noted by the authors)

- (In fact, the 36 sera positive was been assessed by RT-PCR nested and 17 of them were positive 17/36 47.2% line 140)
were also HCV-RNA positive. Ten (58.8%, not the 59.2% noted by the authors)

- Correction done : In fact, 52.9% (9/17)

of these were genotype 1b, 6 were 2b and one was 2a.

- Corrected after new analysis lines 142-143. In this corrected paper, we reduced the genotype presentation to genotype 1 and genotype 2 because specific virological information was included in the paper published in journal of medical virology.

The assessed risk factors for seropositivity using both univariate and multivariate methods. In univariate analyses anti-HCV was significantly associated with age, hospitalization, previous injections, dental treatment, scarification (although the data and P value in table 2 suggest this is not significant),

- corrected after new analysis line 148

IV drug use (although this was rare), and abnormal AST and ALT (which I prefer to ASAT and ALAT which they use).

- corrected lines 28,165,166,173; tables 1,2,3

Multivariate analysis showed that only age and AST were independently associated with anti-HCV. Although not significant following adjustment, all 25 cases had a history of previously receiving therapeutic injections. Age appears to be such an important risk that when included in the model, other exposures became less important,

The above is what the authors found. It should be included in the abstract and should be the basis of the introduction, methods, results and discussion sections.

Discussions of papers and research that are not directly related to this are not appropriate in a descriptive paper such as theirs. Therefore, this would be best as a precise publication. The most interesting finding is that the prevalence of HCV is low in younger individuals

- this is before described in others studies in African region

in this LDC urban population (although they miss this point) suggesting that either (or both) the reservoir levels of the virus in the blood is locally low or they have been fairly good at following safe medical practices. The low prevalence of those admitting to IV drug abuse and receiving blood transfusions can partially explain this.

Before, I discuss the details of the paper; the authors need to share reference 24.

- reference before shared to BMC
Entitled Hepatitis C virus infection and genotypes in ...., which is in press for the J Medical Virology with the editors since the title describes this paper.

The paper will require considerable editorial work. Some examples of these problems follow:

(1) In abstract, they say Anti-HCV positivity "seemed" to increase with age. It doesn't seem, it does. I do not like their closing two sentences in the abstract, they should present their findings and say something like: "XXXX is a community that has a low prevalence of HCV infection." They can hypothesize why this is the case, but their data certainly doesn't lead to "Research in this field will need to be continued." What does that mean?

- Abstract has been corrected – lines 23-35

(2) In the first sentence of the Introduction they say "Hepatitis C virus (HCV) continues to be a major health burden worldwide." It is a health burden. Sentences that "set the table" for the importance of the paper need to be precise and straightforward since they are only leading the reader to the paper itself. One could also argue that it is not HCV that is the health burden, but it is the disease it causes, which is usually called hepatitis C. However, we often interchange the agents and the diseases they cause. Towards the end of the same paragraph, the authors use "anti-HCV Ab". Since this is the first time the use this word, I believe they should use "antibodies to HCV (anti-HCV)."

- Introduction corrected – lines 38-43

(3) Methods. In the statement were they describe the city, "of which it occupies only a small part" adds nothing but words.

- deleted line 67

Since they are the basis of study, I think they need more description of their methods for detecting HCV antibodies and RNA

- methods corrected lines 105-107

I assume that the Desican Plus HCV assay is like a RIBA, but do not know that for sure.

- Line 104

(Also I would be interested to know the results of the testing for HCV-RNA on the 8 serum samples that were indeterminate by the test with exclusion of these patients).

- line 140 – On the 8 serum indeterminate, one was positive by RT-PCR

It is inadequate to describe the test use for "... screened for viral RNA as described previously" when the paper has not been published. Did they use RT-PCR?

- RT-PCR Nested was used

They don't define the type of test they used. They also need to include something about their genotyping methods.

- Methods corrected

- At the moment the paper has been published. We have found one patient indeterminate by Deciscan positive by RT-PCR line 140.

In the analysis, the same results have been found when this patient indeterminate by Deciscan but positive by RT-PCR was included in cases definition.

(4) Results could be made more concise. The figure should be dropped

- done
and the numbers and percentages of anti-HCV (and HCV-RNA) positives and total in the group could be added to table 2.

- we presented result in a new table 1 with risk factor in relation with age group

This marked increase with age, with a maximum of only one case less than 24 years old, strongly suggests a cohort effect which they deny without explaining. They don't show the data but what is seen is that exposures are occurring in older adults that or not occurring in children and young adults and/or exposures occurred in the past that are not occurring recently.

The same result in relation with age was found in 1994 in Madagascar and in others African region. Given the low transmission of HCV through sexual contact, the indication of rising prevalence with age supports the view that unsterile injections and other iatrogenic routes of transmission may be the main risk factor for HCV infection in Africa (Madhava et al). Besides, all HCV positive subjects described a past history of therapeutic injection, furthermore the risk of HCV positivity increase with the number of injections. So cohort effect must be rule out with data showed in new table 1. We prefered the cumulative effect according to the number of therapeutic injections (line 196)

I have already made the point about injections being universal in those who were anti-HCV positive although when adjusted for age and the fact that a large proportion of those not having anti-HCV also had injections, it is not a significant risk. That does not mean that many of those infected were infected by medical injections (see above)

Table 1 provides considerable useful information. It could be more precisely described in the results (results corrected lines 144-170). All the specific data must not be in both places.

2.

(5) Discussion. The data presented here does not warrant an extensive discussion of the prevalence of anti-HCV in other countries or what are the factors for transmission of HCV in Antananarivo other than mentioning some of the examples of transmission in specific areas, particularly in Africa and some thoughts on the transmission pattern. That is why it is now so low in those under age 24. For instance, has the local health department put a strong campaign in past 15-or-20 years that reduced transmission of blood-borne infections. How does this relate to HIV transmission?

Discussion corrected lines 179 -182

HIV prevalence is very low in Madagascar despite high STI prevalence rate and lack of preventive policy. So it’s difficult to relate HIV and HCV transmission.

The way they present their study design and the data analysis is very good and this component appears to be outstanding. I think this paper could be a contribution as a short description of the prevalence of HCV in Antananarivo, IF IT DOES NOT INCLUDE THE SAME MATERIAL IN THE PAPER THAT IS IN PRESS FOR THE JOURNAL OF MEDICAL VIROLOGY.

The paper published in journal of medical virology only focuses the virological characteristics, it’s a contribution on HCV genotype distribution. This paper is based on the epidemiological study and focuses the HCV risk factor.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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

see above

Discretionary Revisions (which the author can choose to ignore) none

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have no competing interests.
Reviewer's report - Response

**Title:** Seroprevalence of hepatitis C and associated risk factors in urban areas of Antananarivo, Madagascar.

Version: 1 Date: 30 October 2007

Reviewer: Flor Pujol

Reviewer's report:

General

This well conducted study reports the prevalence of HCV infection in Antananarivo, Madagascar, with correlation with risk factors associated with HCV transmission and infection.

**Major Compulsory Revisions** (that the author must respond to before a decision on publication can be reached)

1. **Introduction** describes a somehow randomly selected reference of HCV prevalence around the world. It should focus more on describing the prevalence in the African continent with selected comparisons with other continents. The following review: “Madhava V, Burgess C, Drucker E. Epidemiology of chronic hepatitis C virus infection in sub-Saharan Africa. Lancet Infect Dis. 2002; 2:293-302” is suggested as guideline.

   Introduction have been revised using this reference as guideline - lines 48 to 56
   Madhava et al. ref nº14 – lines 320-321

2. By univariate analysis, several risk factors were significantly associated with the presence of HCV antibodies. However, by multilogistic regression analysis, only age and transaminases were significantly associated. Nevertheless, discussion is focused on the practice of unsafe injections. This part should be revised and shortened.

   Given the low transmission of HCV through sexual contact, the indication of rising prevalence with age supports the view that unsterile injections and other iatrogenic routes of transmission may be the main risk factor for HCV infection in Africa (Madhava et al). Besides, all HCV positive subjects described a past history of therapeutic injection, furthermore the risk of HCV positivity increase with the number of injections. So it appeared us important to focus the discussion on the practice of unsafe injections. However we dropped of this part in discussion.

3. For some of the risk factors, a significant lower number of individual information was available. This might have affected the relevance of the risk factor and should be discussed.

   This point have been discussed in the corrected manuscript: lines 186-187

4. Previous scarification is reported as significantly associated with HCV seroprevalence (page 8, line 7). However, p value in Table 1 does not support this statement.
It’s a mistake. This point has been corrected after new analysis. Scarification was not significantly associated with HCV seroprevalence: line 27, line 149

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. The genotyping of HCV positive samples is not mentioned in Methods. 
   **Methods corrected : lines 105-109**

2. Were the serum samples negative or indeterminate by Deciscan tested individually by PCR?
   **All 36 Monolisa positive were tested by PCR - line 139-140**

3. ALT and AST should be used instead of ALAT and ASAT throughout the text.
   **Corrected in manuscript: lines 28,165,166,173; tables 1,2,3**

4. Blood transfusion was not found significantly associated with the presence of HCV antibodies, although previously reported by another group as a significant risk factor in the country. This discrepancy should be discussed.
   **Corrected in discussion of the manuscript : lines 221-235**

5. Reference to HCV genotype distribution in the world is again randomly selected. This information should be described briefly but more comprehensively.
   **Corrected in discussion of the manuscript : lines 245-248 and reference32,33,34**

Discretionary Revisions (which the author can choose to ignore)

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