OPEN PEER REVIEW

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Peer Review Report for "Treatment Coverage and Drug Expenditure in Hepatitis C Patients From 2013 to 2019: A Journey of Improving Treatment Accessibility in Malaysia Through Government-led Initiatives"

Author(s): Huan-Keat Chan, Mohamed Azmi Hassali, Rosaida Md Said, Muhammad Radzi Abu Hassan

Review Timeline:

Submit Date:	10 Jul 2020
Revised Date:	26 Aug 2020
Accepted Date:	9 Oct 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Sofia Bartlett: Reviewer | Revision (0) 24 Jul 2020

Dear AE,
This is a well written and interesting manuscript, where the authors have taken data from public hospitals and primary care clinics in Malaysia to estimate the total number of people treated for HCV infection each year from 2013-2019, estimating the overall drug expenditure cost for these treatments, and the expenditure as a percentage of overall government health expenditure. There are a number of comments that I believe should be addressed before this manuscript is suitable for publication.
Abstract Section:
Please revise the following minor grammatical errors;
- States "Hepatitis C has been a public health threat," this should be in present tense i.e. "Hepatitis C is a public health threat,"
- States "affecting approximately 2.5% of the Malaysia population" this should read "affecting approximately 2.5% of the Malaysian population"
- States "MOH in endeavors driven by non-for-profit organizations" this should read "MOH in

endeavors driven by not-for-profit organizations" OR "MOH in endeavors driven by non-profit organizations"

Background Section:

- The abbreviation CHC is used in paragraph one and this hasn't been previously defined.

Materials and Methods Section:

1. Can you please add a comment here to specify if this sample of 144 public hospitals and 33 public primary health care centers (PHC) is ALL the public hospitals and PHC where HCV treatment is offered in Malaysia? Or add what is the percentage of all HCV treatment centers in Malaysia that this sample represents?
2. Please add a comment here on treatment eligibility criteria for publicly funded HCV treatment in Malaysia (i.e. do people need to sign up for public drug benefits? Are there any fibrosis stage restrictions? etc.)
3. Can you please clarify why you chose 330,000 as the number of HCV infected people in Malaysia? In the introduction, you state that the prevalence of HCV infection in Malaysia is 2%, which should give about 652,000 people living with HCV in Malaysia based off population in 2019.
4. Did the denominator (330,000) have the number of people who received HCV treatment and achieved SVR each year subtracted from it in the subsequent year? If not, then the proportion of HCV treatment uptake overall for each year in Table 1 is not accurate and may be an underestimate, assuming there are not large numbers of new HCV infections each year.

Discussion:

- You've referenced the Malaysian Government and MOH efforts to increase HCV treatment uptake and work towards the WHO HCV elimination goals, however it would seem that as of 2019, Malaysia is very far off-track on achieving these targets by 2030, and this hasn't really been commented on in this manuscript. While you've indeed demonstrated that the number of patients receiving HCV treatment has grown more than 10 times since 2013, can you comment on how many more times this number needs to grow to reach the number of treatment initiations needed per year to reach the target of 80% of people with chronic HCV treated by 2030? My "back of the envelope calculation" is that if a total of 6,300 people have been treated, there are a further 323,700 people in Malaysia requiring HCV treatment, and 80% of this would be 258,960 people. If we divide this by 10 to estimate how many people need to be treated per year from 2020-2030, it's about 25,896 people per year. Only 3,116 people were treated in 2019, therefore annual treatment uptake needs to increase by more than 8 fold during just 2020.
- Given the above, can you also please comment if this scale of increasing HCV treatment uptake seems achievable given the current costs of HCV treatment, Malaysian government health spending budgetary pressure, and health infrastructure?

Thanks.

REFEREE: Associate Editor | **Revision (0)** 14 Aug 2020

The manuscript entitled “Treatment Coverage and Drug Expenditure in Hepatitis C Patients from 2013 to 2019: A Journey of Improving Treatment Accessibility in Malaysia through Government-led Initiatives” was reviewed by an expert reviewer in the field and myself. Both of us believed that there is potential in these data to contribute to the literature, however,

there are major concerns about the methodology and interpretation of the data with potential impact on the validity of the findings. More detailed comments have come below and also under the reviewer's comments. The authors need to address all of the comments and revise the manuscript accordingly. The revised manuscript will be reviewed. The final decision would be based on reviewing the revised version with no guarantee of acceptance.
1- On several occasions in the manuscript, the reference used do not look relevant to the states for which it has been used. For example, in the Introduction, the authors stated "Liver cirrhosis and hepatocellular carcinoma are among the fatal complications of CHC, claiming nearly 400,000 lives annually". It is a global estimate, but one of the references (reference #4) is a Brazilian study. The authors need to make sure to use the most relevant references for their statements.
2- Methods (page 4): "The treatment coverage was summarized as the percentage of new patients who received hepatitis C treatment in a particular year, using the estimated number of HCV-infected individuals in Malaysia (n=330,000) as the denominator (6)". It is not clear how the number of people with HCV has been estimated. Reference #6 has not reported any data relevant to this statement.
3- Results (page 4): "Over the course of 7 years, a total of 6,368 hepatitis C patients seeking care". I was wondering if these 6,368 patients were unique patients or some received more than one treatment course during this period. Is there any data of patients who received more than one treatment course due to treatment failure or reinfection?
4- Results (page 4): "A significant linear association is found between the time and the growth of the number of patients treated ($P<0.001$)". Using a linear regression model is not the best option given the numbers clearly show an exponential increase in treatment uptake rather than a linear increase. Moreover, the increasing treatment uptake is very obvious and no statistical significance is required to prove the increase. The authors are recommended to remove this sentence. They should also revise the methods and remove the parts about using linear regression.
5- Table 1: It would be more informative for the general audience if the authors report the cost in US dollar or Euro in addition to MYR.
Thanks.

Seyed Moayed Alavian: EIC | **Revision** (**0**) 17 Aug 2020

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

LETTER TO THE EDITOR AND REVIEWER

Dear Editor and Reviewers,

We appreciate your time and efforts in reviewing this manuscript. All the corrections made in the manuscript and tables are highlighted in red. Besides, we have addressed all issues indicated in the review report as follows:

A. Comments of Reviewer 1

1. *This is a well written and interesting manuscript, where the authors have taken data from public hospitals and primary care clinics in Malaysia to estimate the total number of people treated for HCV infection each year from 2013-2019, estimating the overall drug expenditure cost for these treatments, and the expenditure as a percentage of overall government health expenditure. There are a number of comments that I believe should be addressed before this manuscript is suitable for publication.*

   Response: Thank you. Your response to our work is encouraging. All your comments are addressed accordingly.

2. *Abstract Section:*
   (a) Please revise the following minor grammatical errors;
   - States "Hepatitis C has been a public health threat," this should be in present tense i.e. "Hepatitis C is a public health threat,"
   - States "affecting approximately 2.5% of the Malaysia population" this should read "affecting approximately 2.5% of the Malaysian population"
   - States "MOH in endeavors driven by non-for-profit organizations" this should read "MOH in endeavors driven by not-for-profit organizations" OR "MOH in endeavors driven by non-profit organizations"

   Response: Corrections are made (refer to the abstract).

3. *Background Section:*
   (a) The abbreviation CHC is used in paragraph one and this hasn't been previously defined.

   Response: Definition is added (refer to paragraph 1 of Background).

4. *Materials and Methods Section:*

(a) *Can you please add a comment here to specify if this sample of 144 public hospitals and 33 public primary health care centres (PHC) is ALL the public hospitals and PHC where HCV treatment is offered in Malaysia? Or add what is the percentage of all HCV treatment centres in Malaysia that this sample represents?*

Response: The sentence is rephrased (refer to abstract and paragraph 1 of Materials and Methods). This number represents all the public health institutions which provided hepatitis C treatment during the study period.

(b) *Please add a comment here on treatment eligibility criteria for publicly funded HCV treatment in Malaysia (i.e. do people need to sign up for public drug benefits? is there any fibrosis stage restrictions? etc.)*

Response: A sentence is added to emphasize that "the patients were treated at the discretion of physicians despite their liver fibrosis stages". Also, the sources of funding is added (refer to paragraph 1 of Materials and Methods).

Response:

(c) *Can you please clarify why you chose 330,000 as the number of HCV infected people in Malaysia? In the introduction, you state that the prevalence of HCV infection in Malaysia is 2%, which should give about 652,000 people living with HCV in Malaysia based off population in 2019.*

Response: To more accurately predict the prevalence of hepatitis C in Malaysia, we adopt the most recent findings from a large-scale, community-based screening program. The estimated number of hepatitis C patients in 2019 is, therefore, corrected to be 619,400 (1.9% of a population of 32.6 million) (refer to abstract and paragraph 2 of Materials and Methods).

(d) *Did the denominator (330,000) have the number of people who received HCV treatment and achieved SVR each year subtracted from it in the subsequent year? If not, then the proportion of HCV treatment uptake overall for each year in Table 1 is not accurate and may be an underestimate, assuming there are not large numbers of new HCV infections each year.*

Response: We revisit the way we estimate the number of patients each year, taking account of the number of patients who were not yet treated and had achieved SVR in the preceding years, as well as the annual incidence and mortality rates of HCV (refer to paragraph 2 and 3 of Materials and Methods).

5. *Discussion*

(a) *You've referenced the Malaysian Government and MOH efforts to increase HCV treatment uptake and work towards the WHO HCV elimination goals, however it would seem that as of 2019, Malaysia is very far off-track on achieving these targets by 2030, and this hasn't really been commented on in this manuscript. While you've indeed demonstrated that the number of patients receiving HCV treatment has grown more than 10 times since 2013, can you comment on how many more times this number needs to grow to reach the number of treatment initiations needed per year to reach the target of 80% of people with chronic HCV treated by 2030? My "back of the envelope calculation" is that if a total of 6,300 people have been treated, there are a further 323,700 people in Malaysia requiring HCV treatment, and 80% of this would be 258,960 people. If we divide this by 10 to estimate how many people need to be treated per year from 2020-2030, it's about 25,896 people per year. Only 3,116 people were treated in 2019, therefore annual treatment uptake needs to increase by more than 8 fold during just 2020.*

Response: We completely share your view. Please refer to paragraph 6 of the discussion, which addresses this issue and highlights the efforts made by the MOH to scale up the hepatitis C screening and treatment in Malaysia. With that, we also slight revised the conclusion.

(b) *Given the above, can you also please comment if this scale of increasing HCV treatment uptake seems achievable given the current costs of HCV treatment, Malaysian government health spending budgetary pressure, and health infrastructure?*

Response: We address this issue in paragraph 7 of the discussion, mainly by highlighting the special allocation made by the MOH to support the hepatitis C program. Following the changes, we also slight revised the conclusion.

B. Comments of Associate Editor

1. *The manuscript entitled "Treatment Coverage and Drug Expenditure in Hepatitis C Patients from 2013 to 2019: A Journey of Improving Treatment Accessibility in Malaysia through Government-led Initiatives" was reviewed by an expert reviewer in the field and myself. Both of us believed that there is potential in these data to contribute to the literature, however, there are major concerns about the methodology and interpretation of the data with potential impact on validity of the findings. More detailed comments have come below and also under the reviewer's comments. The authors need to address all of the comments and revise the manuscript accordingly. The revised manuscript will be reviewed. The final decision would be based on reviewing the revised version with no guarantee of acceptance.*

   Response: Thank you for your insightful comments. The manuscript is revised accordingly.

2. *On several occasions in the manuscript, the reference used do not look relevant to the statement for which it has been used. For example, in the Introduction, the authors stated "Liver cirrhosis and hepatocellular carcinoma are among the fatal complications of CHC, claiming nearly 400,000 lives annually". It is a global estimate, but one of the references (reference #4) is a Brazilian study. The authors need to make sure to use most relevant references for their statements.*

   Response: Reference #4 is removed. We have double-checked the references and ensured that they are relevant to the statements for which they are used.

3. *Methods (page 4): "The treatment coverage was summarized as the percentage of new patients who received hepatitis C treatment in a particular year, using the estimated number of HCV-infected individuals in Malaysia (n=330,000) as the denominator (6)". It is not clear how the number of people with HCV has been estimated. Reference #6 has not reported any data relevant to this statement.*

   Response: We replace Reference #6 with Reference #7, which depicts a recent nationwide, large-scale screening program in Malaysia. It shows that approximately 1.9% of the Malaysian population (n=619,400) was infected with HCV in 2019. This number is also used to estimate the number of HCV-infected patients from 2013 to 2018 in this study, taking account of the number of patients who were not yet treated and had achieved SVR between this period, as well as the annual incidence and mortality rates of HCV (refer to paragraph 2 and 3 of Materials and Methods).

4. *Results (page 4): "Over the course of 7 years, a total of 6,368 hepatitis C patients seeking care". I was wondering if these 6,368 patients were unique patients or some received more than one treatment course during this period. Is there any data of patients who received more than one treatment course due to treatment failure or reinfection?*

   Response: The number 6,368 includes interferon-experienced patients who were retreated with. To better estimate the actual burden of the disease, we, therefore, also present the corrected total number of patients receiving the treatment over the 7-year period, with the estimated number of retreated patients taken into consideration (refer to paragraph 3 of Materials and Methods and paragraph 1 of Results).

5. *Results (page 4): "A significant linear association is found between the time and the growth of the number of patients treated (p<0.001)". Using a linear regression model is not the best option given the numbers clearly shows an exponential increase in treatment uptake rather than a linear increase. Moreover, the increasing treatment uptake is very obvious and no statistically significance is required to prove the increase. The authors are recommended to remove this sentence. They should also revise the methods and remove the parts about using linear regression.*

   Response: The analysis is removed and the methods are revised.

6. *Table 1: It would be more informative for general audience if the authors report the cost in US dollar or Euro in addition to MYR.*

   Response: The cost in US$ is added. The conversion is performed based on the mean exchange rate of each year (refer to paragraph 4 of Materials and Methods and Table 1).

We hope that we have successfully addressed all your comments. Thank you.

Yours sincerely,

Huan-Keat Chan

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 8 Oct 2020

Dear EIC,
The authors have addressed the reviewers' comments properly and have made the required revisions.
Thanks.

Seyed Moayed Alavian: EIC | **Revision** (1) 9 Oct 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.