Author’s response to reviews

Title: A dynamic model and some strategies on how to prevent and control hepatitis C in mainland China

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Author’s response to reviews:

Responses to the Reviewers' Report (INFD-D-18-01089R1)

Dear Editors and Reviewers,

We would like to thank the editors for giving us a chance to resubmit our manuscript, and also thank the reviewers for giving us constructive suggestions which would help us both in English and in depth to improve the quality of the paper. We will submit a new version, which has been modified according to the reviewer’s suggestions. Efforts were also made to correct the mistakes and improve the English of the manuscript. Detailed responses will be listed in the following.

We have many changes in the manuscript as following.

1. We reformat our Declarations section according to submission guidelines. We added ‘Funding’, ‘Availability of data and materials’, ‘Ethics approval and consent to participate’ and ‘Consent for publication’, as stated in Page 13 and 14.

2. We reformat headings of the paper to ‘Background’, ‘Methods’, ‘Results’, ‘Discussion’ and ‘Conclusions’ according to submission guidelines.

3. We have added ‘Abbreviations’ after the conclusion of the text, as stated in Page 13.

4. Due to the modification of the headings number, we made corresponding modifications in the
paper about the headings number. For example, we change the world ‘sixth’ into ‘fifth’ at page 9, line 5 and the last paragraph of Background.

5. We change the sentence ‘the fit results will better’ into ‘the fit result will be better’, as stated in Page 3, line 21.

6. We change the word ‘has’ into ‘is’ in the first paragraph under the Model Formulation, as stated in Page 3, line 24.

7. Under Parameter estimation, page 6, line 16, it’s our mistake that we miscalculated the total population which the correct value is.

8. We change the sentence ‘chronic infection transmit HCV to others is the most important factor’ into ‘transmission of HCV from exposed and infection to others is the most important factor’, as stated in Page 8, line 22.

9. We delete a world ‘in’ at page 8, line -5.

10. We add the number 3 at the end of the Table, page 8, line -9 under the Sensitivity analysis of.

11. We change the sentence ‘The detail calculation …and λ’ into ‘The detail calculation of sensitivity indices of endemic equilibrium are shown in Appendix A and values are given in Table 4 by using the parameters values of 2015 given in Table 2. We can see that: the most sensitive parameter for is followed by and’, as stated in Page 9, lines -11.

12. We change the sentence in the Discussion " the reason is as follows" into "the reasons are as follows " And as stated in Page 10, line -1.

13. We change the word ‘have’ into ‘has’ in the third and fifth paragraph under the Discussion, as stated in Page 11, line 3 and 8.

14. We have revised some sentences in the Conclusion:
   (1) " Reducing infection rate …the spread of the HCV (see Fig. 3)." into "It can control the spread of the HCV by reducing infection rate of contacting with the exposed and the acutely infected to the susceptible and (see Fig. 3)." And as stated in Page 11, lines -1~4.
   (2) " Shortening the diagnosis time …the spread of HCV at a lower level (see Fig. 3)." into " It can control the spread of HCV at a lower level by shortening the diagnosis time of acute infection () and the hesitant time for being treated of chronically infected patients () (see Fig. 3)." And as stated in Page 12, lines 4~7.
   (3) " Reducing the diagnosis time …control the spread of HCV (see Fig. 3) " into " It can effectively control the spread of HCV by reducing the diagnosis time of exposed (), i.e., improve the rate of progressing to acute stage from the exposed stage () (see Fig. 3)" And as stated in Page 11, lines 14~17.
   (4) " Improving recovery rate …a relatively small size " into " It can control the number of patients in a relatively small size by improving recovery rate of hospitalization ." And as stated in Page 12, lines -12~10.

15. In addition, we have also corrected many words, grammatical errors, detailed corrections can be seen in the revised version (Hepatitis C model((Highlighted in yellow)).pdf).
The following is a point-to-point response to the two reviewers' comments and suggestions.

Responses to the comments of Reviewers

Based on the comments of reviewers, we give the following responses.

Reviewer #1:

Abstract: It would be better to add some more detail under "Conclusion".

*Response: Thank you for your good suggestion. We have revised some descriptions under "Conclusion": "We find that small changes of transmission infection rate of acutely infected population, transmission infection rate of exposed population, transition rate for the acutely infected, and rate of progression to acute stage from the exposed can achieve the purpose of controlling HCV through sensitivity analysis. Finally, based on the results of sensitivity analysis, we find out several preventions and control strategies to control the Hepatitis C." as stated in Abstract.

Background

1. Recently (18 July, 2018), the World Health Organization (WHO) estimates that approximately 71 million people have chronic hepatitis C virus (HCV) infection worldwide and approximately 399,000 people die each year after HCV diagnosis, mostly from cirrhosis and hepatocellular carcinoma (HCC) (http://www.who.int/news-room/fact-sheets/detail/hepatitis-c).

*Response: Thanks for your valuable advice. We changed the sentence "The World Health Organization (WHO) estimates that … on account of hepatitis C liver disease" into "Recently (18 July, 2018), the World Health Organization (WHO) estimates that approximately 71 million people have chronic hepatitis C virus (HCV) infection worldwide and approximately 399,000 people die each year after HCV diagnosis, mostly from cirrhosis and hepatocellular carcinoma (HCC)". And as stated in Page 1, Background, Paragraph 1, lines 1-4. Meanwhile, we change the first reference into "http://www.who.int/news-room/fact-sheets/detail/hepatitis-c".


*Response: Thanks for your valuable advice. We changed the sentence "In the United States, an estimated … HCV-associated chronic liver disease." into "An estimated 3.5 million people in the United States (US) has chronic hepatitis C. In 2016, there are 18,153 hepatitis C-related deaths in the US which is lower than from 2012 to 2015 (18,650 to 19,629)". And as stated in Page 1, Paragraph 1, lines 4-5. At the same time, we changed the reference to the two recommended by the reviewer.

3. In the European region, approximately 14 million people are chronically infected with HCV, representing about 20% of the global burden of disease due to HCV infection (http://www.euro.who.int/__data/assets/pdf_file/0009/377253/fact-sheet-hepatitis-c-eng.pdf).

*Response: Thanks for your valuable advice. We changed the sentence "In addition, the prevalence of HCV in Europe is about 1% among the crowd" into "In the European region, approximately 14 million people are chronically infected with HCV, representing about 20% of the global burden of disease due to HCV infection". And as stated in Page 2, line 1. At the same time, we changed the reference to the recommended by the reviewer.


*Response: Thanks for your valuable advice. We changed the sentence "Hepatitis C virus was discovered in 1989" into "HCV was discovered in 1989 by Choo et al.". And as stated in Page 2, Paragraph 2, line 1. At the same time, we changed the reference to the recommended by the reviewer.

5. On line 39, the authors have added ‘following acute infection, chronic hepatitis could be ensured 13.7 + 10.9 years later, chronic active hepatitis could be ensured 18.4 + 11.2 years later, cirrhosis of the liver could be ensured 20.6 + 10.1 years later, and hepatocellular carcinoma could be ensured in 28.3 + 11.5 years’. These results are not found in this reference ‘Thomson BJ, Finch RG, Hepatitis C virus infection, Clin. Microbiol. Infect. 2005; 11: 86-94’.


Please make changes.


Model
2.2 Model Formulation

Figure 1: Regarding acutely infected individuals (Ia), would it be ρ1α instead of ρ2α and progress to the chronic stage with the ratio (Ic), would it be ρ2δ instead of ρ1δ?

*Response: As for the reviewer’s concern, we examined the flowchart in figure 1 and the formula in model (2.1) carefully and found that the fifth differential equation in model (2.1) was wrong. This is our mistake, so we change the fifth differential equation into , In addition, we have also modified Figure 1, as stated in Page 4.

2.3 Parameter estimation

Are these values correct?

‘Where, the optimal values of parameters are listed in Table 2, and the each initial condition from 2011 to 2016 is fixed as (4.23 x 107, 3.81 x 105, 100, 7.46 x 104, 469, 4.08 x 107), (3.66 x 107, 8.54 x 104, 116, 3.08 x 104, 436, 1.10 x 107), (9.01 x 107, 4.18 x 105, 118, 105, 653, 4.80 x 107), (7.07 x 107, 4.64 x 105, 6.51 x 104, 6.12 x 104, 577, 8.98 x 107), (5.36 x 107, 3.48 x 105, 9.10 x 104, 6.17 x 104, 698, 4.52 x 107), (2.66 x 107, 9.71 x 105, 100, 8.81 x 104, 646, 5.83 x 107)’.

*Response: As for the reviewer’s concern, we made the following explanation after careful review of relevant information. We found the optimal parameter values and the initial values of the model in 2011 after continuous debugging, then, using the optimal parameter values of the model in 2011 as the starting value, we have found the optimal parameter values of each subsequent year through continuous simulation. Meanwhile, we present this explanation in the paper, as stated in Page 6, line10-14.

Sensitivity analysis of

Line 22-25: The authors reported that ‘The sensitivity indices and corresponding % value needed to affect a 1% decrease inare shown in Table 3 (e.g., in order to decrease in the value of by 1% it is necessary to decrease the value of β2 by 1.1945%......’. On Table 3, β2 Corresponding % changes reported as ‘-1.7945’. Please change it accordingly.

*Response: Thank you very much for keenly pointing out this mistake. We change the number
"1.1945%" into "1.7945%". And as stated in Page 8, line-4.

Minor comments
1. It would be good to include definitions under Table 1 parameters, Table 2 and Figure 1. Also include definition for ‘HFMD’.
   *Response: Thank you for your good suggestions. We added the definition of the number of infected during the initial patient’s infectious (not sick) period’ in the parameters column of table 1 which is stated in Page 5, Table 1. As to HFMD, we wrote HCV as HFMD mistakenly, this is our mistake. So, we change the word "HFMD" into "HCV". And as stated in Page 12, line 14.

2. Please change Reference numbers. In the text they should be [1], [2] instead of [3], [3-5] instead of [4-6], [6] instead of [9], [7], etc. e.g. Reference #2 should be after Reference #10 and this link ‘https://www.healthline.com/health/hepatitis-c-incubation-period’ is an error. Please use this link which is available: ‘https://www.healthline.com/health/hepatitis-c-incubation-period#2’.
   *Response: Thank you for your good suggestion. We have renumbered the references in the order in which they appear in the paper.

3. Under ‘Background’, line 15, ribonucleic acid (RNA) to add.
   *Response: Thank you for your good suggestion. We add the world "ribonucleic acid" under ‘Background’, Page 2, line 6.

4. References to change. For example:
   *Response: Thank you for your good suggestion. We have reorganized the references according to the criteria presented by the reviewer.

5. Also add page numbers.
   *Response: Thank you very much! We add the page numbers in the References.

Reviewer #2: PEER REVIEWER ASSESSMENTS
OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective
DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are minor issues
EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
No - there are minor issues
STATISTICS - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
No - there are minor issues

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions

GENERAL COMMENTS:
The authors present a mathematical model of the epidemiology of HCV in mainland China and use it to indicate some preventive measures to stop spreading the disease.

(1) The authors used data available from Chinese CDC and estimated most of the parameters of the model using an optimization function (fmincon) from Matlab. It would be more useful if all the information needed to call this function was provided, as for example, the algorithm that is used and how they chose the lower and upper boundaries.

*Response: Thank you for your good suggestions. We have written a paragraph to explain the algorithm of fmincon function, hoping readers will be able to understand our methods better. ‘Fmincon function is a Matlab function for solving the minimum value of constrained nonlinear multivariate function. Fmincon implements four different algorithms: interior point, sequence quadratic program (SQP), active set, and trust region reflective. In this paper, we choose the SQP algorithm to solve the optimal solution of model (2.1). MATLAB SQP method is divided into three steps: firstly, update the Lagrangian Hessian matrix, then solve the quadratic programming problem, and finally calculate the one-dimensional search and objective function.’ And as stated in Page 6, lines-12~-8.

According to the epidemiological characteristics of hepatitis C and the biological significance of the parameters, we set the lower and upper boundaries of each parameter, as shown in table 1. And as stated in Page 6, lines-8~-6.

(2) The model reproduces well the data except from some data points that seems to be outliers (Fig 2.) The authors explain that it could be an outbreak but there is no explanation of why the model is not able to capture that outbreak.

*Response: Thanks for your valuable advice. Our model is based on the ideal state, without considering the impact of unexpected events, so the model is not able to capture that outbreak. Meanwhile, we present this explanation in the paper, as stated in Page 6, lines8~10.

(3) In general, the paper is well organized and the objective and conclusions are clear to understand. The methods section would be improved with detailing of the function fmincon as suggested.

*Response: Thank you for your good suggestions. We have written a paragraph to explain the algorithm of fmincon function, hoping readers will be able to understand our methods better. ‘Fmincon function is a Matlab function for solving the minimum value of constrained nonlinear multivariate function. Fmincon implements four different algorithms: interior point, SQP, active set, and trust region reflective. In this paper, we choose the SQP algorithm to solve the optimal solution of model 2.1. MATLAB SQP method is divided into three steps: firstly, update the Lagrangian Hessian matrix, then solve the quadratic programming problem, and finally calculate the one-dimensional search and objective function.’ And as stated in Page 6, lines-12~-8.

(4) Regarding results, Figure 2 should be better explained in relation to the modeling and parameter estimation.

*Response: Thank you for your good suggestion. We have written a paragraph to explain Figure 2,
hoping readers will be able to understand better. ‘The values of the various parameters in Table 2 are in days. We calculated the numbers of the treated in each month of each year according to the optimal simulation parameters, then, compared it with the reported hepatitis C data in China from 2011 to 2016 per month. We use two broken line diagrams, as shown in Fig. 2.’ as stated in Page 8, lines 1–4.

(5) The authors did not explain their choice for estimating parameters for each year.
*Response: Thank you for your good suggestion. As for the reviewer’s concern, we made the following explanation after careful review of relevant information. ‘Although the outbreak of hepatitis C is not seasonal, it still has a certain periodicity. Our model does not have a periodic solution, so we can only simulate the annual parameter values separately.’ And as stated in Page 6, lines -6--4.

(6) Why there are different sets of parameters for each year?
*Response: As for the reviewer’s concern, we made the following explanation after careful review of relevant information. ‘Taking year as the research unit, the parameters of the model (2.1) vary from year to year because of the annually different natural conditions and environmental factors, but the same parameters are not significantly different in different years.’ And as stated in Page 6, lines-3--1.

(7) Table 2 should be better explained in the text. All the choices that the authors made should be clear to the reader. There are also some suggestions regarding the English language that I would also like to send to the authors to improve their text.
*Response: Thank you for your good suggestion. As for the reviewer’s concern, we made the following explanation after careful review of relevant information. Total population is about $1.35 \times 10^9$ in China between 2011 to 2016 [28], We chose 80% of the population as the sampled population, and denote as $\tilde{N} = 1.08 \times 10^9$. And as stated in Page 6, Section 2.3 , lines 7~9.

REQUESTED REVISIONS:
(8) The authors should address the choices they made regarding the experiments, better explaining the reasons for fitting parameter per year (Table 2).
*Response: Thank you for your good suggestion. As for the reviewer’s concern, we made the following explanation after careful review of relevant information. Although the outbreak of hepatitis C is not seasonal, it still has a certain periodicity. Our model does not have a periodic solution, so we can only simulate the annual parameter values separately. And as stated in Page 6, lines -6--4.

(9) Moreover, they should also better explain Figure 2 improving the discussion.
*Response: Thank you for your good suggestion. We have written a paragraph to explain Figure 2, hoping readers will be able to understand better. ‘The values of the various parameters in Table 2 are in days. We calculated the numbers of the treated in each month of each year according to the optimal simulation parameters, then, compared it with the reported hepatitis C data in China from 2011 to 2016 per month. We use two broken line diagrams, as shown in Fig. 2.’ as stated in Page 8, lines 1–4.

ADDITIONAL REQUESTS/SUGGESTIONS:
(10) There are some revisions regarding language that should be addressed before the manuscript can be accepted.
*Response: Thank you for your good suggestion. We have read through the paper, corrected some grammatical errors and rewritten some sentences to make it more authentic.

Dear Editors and Reviewers,
We have tried our best to revise and improve the manuscript and made great changes in the manuscript according to the reviewers’ very good comments. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the corrections will meet with approval. Once again, thank you very much for your comments and suggestions. We look forward to your information about my revised papers and thank you for your good comments.

Sincerely yours

Yong Li