PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatment as prevention for hepatitis C virus in Pakistan: Mathematical modeling projections
AUTHORS	Ayoub, Houssein; Abu-Raddad, Laith

VERSION 1 - REVIEW

REVIEWER	Mark Sonderup University of Cape Town South Africa
REVIEW RETURNED	18-Dec-2018

GENERAL COMMENTS	Thank you for asking me to review this manuscript. The study is clear and looks at whether TasP in Pakistan would aid in achieving the 2030 elimination ideals for hepatitis C. The concept of TasP is now well accepted and understood for at risk groups and modelled for whole countries such as Egypt. Whilst I appreciate this is a modelling paper - the authors may wish to consider the following: 1. Expand upon the reasons or factors driving hep C transmission in Pakistan. Would addressing these factors play an additional role in driving down incidence and prevalence in Pakistan - as an add on to TasP. 2. Perhaps for readers not familiar with Pakistan - explain what the predominant genotype sin Pakistan are and what treatments are envisaged to be used that cost <100$ 3. Does the model rest its cost entirely on the drug costs? If so what about lab and other costs? Will these impact the model as well 4. If currently 311000 people have been treated to date - and the model needs 490000 per year - any suggestions on how to achieve this? Some thoughts here may strengthen the manuscript.

REVIEWER	Huma Qureshi Doctors Plaza, Karachi, Pakistan
REVIEW RETURNED	08-Jan-2019

GENERAL COMMENTS	the paper by Lim was also modeled for 2030 target of hepatitis elimination and suggested to drastically increase the numbers to be treated over years along with prevention of risk factors and prioritizing treatment for high risk populations. At that time DAAs were just introduced in Pakistan and their cost was also not low,

	In this paper, one needs to consider that mathematically it is easier to define a numbers who are infected and divide them over years to set yearly targets, but in reality only 15-20% people know their disease status while others are undiagnosed. There is a huge cost attached to bring them out for testing and treatment. The mathematical analysis of the 5 scenarios describes a better picture of cost per treatment and the long term cost saving by preventing chronic infection and its complications,since the availability of cheaper highly effective generic DAAs in Pakistan.

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments

Reviewer #1:

The study is clear and looks at whether TasP in Pakistan would aid in achieving the 2030 elimination ideals for hepatitis C. The concept of TasP is now well accepted and understood for at risk groups and modelled for whole countries such as Egypt. Whilst I appreciate this is a modelling paper - the authors may wish to consider the following:

Comment: We thank the reviewer for reviewing our work, constructive feedback, and the valuable feedback and suggestions that have enriched this article and improved its readability. Please find below replies addressing each of the reviewer's comments.

1. Expand upon the reasons or factors driving hep C transmission in Pakistan. Would addressing these factors play an additional role in driving down incidence and prevalence in Pakistan - as an add on to TasP.

Answer: We thank the reviewer for these valuable suggestions. Extensive evidence demonstrates that most ongoing HCV transmission in Pakistan is driven by various healthcare-related procedures, such as therapeutic injections, intravenous infusions, and poor sterilization of medical equipment (1-7). As for the second point, indeed HCV-TasP needs to be supplemented with prevention in all segments of the healthcare system to accomplish the HCV elimination target by 2030.

To address the reviewer's suggestions, we have now expanded on these points and clarified them in the revised manuscript (Discussion, page 11, third paragraph and page 12, first paragraph).

2. Perhaps for readers not familiar with Pakistan - explain what the predominant genotype sin Pakistan are and what treatments are envisaged to be used that cost <100$

Answer: We thank the reviewer for the useful suggestions. Based on a recent systematically-assembled and large database of HCV data from Pakistan, genotype 3 was found to be the most common genotype in all of Pakistan's provinces (7). As for treatment regimens, generics for different direct acting antivirals (DAAs) (e.g. sofosbuvir) have been introduced and are being manufactured in Pakistan at a cost of <$100 (8).

To address the reviewer's suggestions, we have now clarified the predominant genotype in Pakistan (Introduction, page 4, first paragraph), and the main HCV treatment regimen used at a cost of <$100 (Introduction, page 4, second paragraph).

3. Does the model rest its cost entirely on the drug costs? If so what about lab and other costs? Will these impact the model as well

Answer: We thank the reviewer for the valuable comment. The cost per infection averted includes only the cost of the drug and its direct implementation, but it does not include the cost of screening/testing to identify the chronically-infected individuals. Future work needs to explore the cost-effectiveness of combined HCV testing and treatment programs.

To address the reviewer's comment, we have now clarified this point in the revised manuscript (Discussion, page 12, second paragraph).

4. If currently 311000 people have been treated to date - and the model needs 490000 per year - any suggestions on how to achieve this? Some thoughts here may strengthen the manuscript.

Answer: We thank the reviewer for the pertinent comment. This is the core and most pressing question of HCV response in Pakistan today. A key challenge is that most chronically-infected individuals are unaware of their infection. Therefore, there is no escape from the development of a national testing program that is guided by epidemiological data.

A recent study provided a conceptual map for such testing program with focus on Pakistan and Egypt (9). The study showed that testing strategies can be much more efficient through population prioritization by risk of exposure. For example, testing efficiency was highest by targeting, respectively, populations with liver conditions, people who inject drugs, populations with high-risk health care exposures, and special clinical populations, where only 2-4 tests would be needed to identify a chronic infection, followed by populations at intermediate risk, and eventually general populations.

To address the reviewer's comment, we have now added a paragraph to clarify this issue along the lines discussed here (Discussion, page 11, second paragraph).

Reviewer #2:

Comment: We thank the reviewer for reviewing our work and the constructive feedback. We also appreciate the reviewer's valuable suggestions and comments that have enriched this article. Please find below replies to the reviewer's comments and suggestions.

1. The paper by Lim was also modeled for 2030 target of hepatitis elimination and suggested to drastically increase the numbers to be treated over years along with prevention of risk factors and prioritizing treatment for high risk populations. At that time DAAs were just introduced in Pakistan and their cost was also not low, In this paper, one needs to consider that mathematically it is easier to define a numbers who are infected and divide them over years to set yearly targets, but in reality only 15-20% people know their disease status while others are undiagnosed. There is a huge cost attached to bring them out for testing and treatment. The mathematical analysis of the 5 scenarios describes a better picture of cost per treatment and the long term cost saving by preventing chronic infection and its complications, since the availability of cheaper highly effective generic DAAs in Pakistan.

Answer: We thank the reviewer for the valuable comment. We fully agree with the reviewer that the main challenge in Pakistan today is to identify the chronically-infected individuals and to link them with DAA treatment. To this end, a recent study provided a conceptual map for such testing program with focus on Pakistan and Egypt (9). The study showed that testing strategies can be much more efficient through population prioritization by risk of exposure. For example, testing efficiency was highest by targeting, respectively, populations with liver conditions, people who inject drugs, populations with high-risk health care exposures, and special clinical populations, where only 2-4 tests would be needed to identify a chronic infection, followed by populations at intermediate risk, and eventually general populations.

To address the reviewer's comment, we have now added a paragraph to clarify this issue along the lines discussed here (Discussion, page 11, second paragraph).

References

1. Aslam M, Aslam J, Mitchell BD, Munir KM. Association between smallpox vaccination and hepatitis C antibody positive serology in Pakistani volunteers. Journal of Clinical Gastroenterology. 2005;39(3):243-6.

2. Abbas Z, Jeswani NL, Kakepoto GN, Islam M, Mehdi K, Jafri W. Prevalence and mode of spread of hepatitis B and C in rural Sindh, Pakistan. Tropical gastroenterology : official journal of the Digestive Diseases Foundation. 2008;29(4):210-6.

3. Idrees M, Lal A, Naseem M, Khalid M. High prevalence of hepatitis C virus infection in the largest province of Pakistan. Journal of Digestive Diseases. 2008;9(2):95-103.

4. Hashmi A, Saleem K, Soomro JA. Prevalence and factors associated with hepatitis C virus seropositivity in female individuals in Islamabad, Pakistan. International Journal of Preventive Medicine. 2010;1(4):252-6.

5. Ahmed F, Irving WL, Anwar M, Myles P, Neal KR. Prevalence and risk factors for hepatitis C virus infection in Kech District, Balochistan, Pakistan: Most infections remain unexplained. A cross-sectional study. Epidemiology and Infection. 2012;140(4):716-23.

6. Al Kanaani Z, Kouyoumjian SP, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Pakistan: Systematic review and meta-analysis. Royal Society Open Science. 2017;5:180257.

7. Mahmud S, Al Kanaani K, Abu-Raddad LJ. Characterization of the hepatitis C virus (HCV) epidemic in Pakistan. Under review. 2019.

8. Moin A, Fatima H, Qadir TF. Tackling hepatitis C—Pakistan's road to success. The Lancet. 2018;391(10123):834-5.

9. Chemaitelly H, Mahmud S, Kouyoumjian SP, Al-Kanaani Z, Jourmana HG, Abu-Raddad LJ. Who to Test for Hepatitis C Virus in the Middle East and North Africa?: Pooled Analyses of 2,500 Prevalence Measures, Including 49 Million Tests. Hepatology Communications. 2019;In Press.

VERSION 2 – REVIEW

REVIEWER	Mark Sonderup University of Cape Town, South Africa
REVIEW RETURNED	26-Jan-2019

GENERAL COMMENTS	Thank you for the responses. They are adequate. One small suggestion, when suggesting the DAA therapies as you have now added, I would advise it be listed as sofosbuvir and daclatasvir (Introduction, page 4). Currently you have added e.g. generic sofosbuvir Stand alone sofosbuvir should not be used to treat a genotype 3 population

VERSION 2 – AUTHOR RESPONSE

Reviewers' comments

Reviewer #1:

Please leave your comments for the authors below

Thank you for the responses. They are adequate.

Comment: We thank the reviewer for reviewing our work, constructive feedback, and the valuable feedback and suggestions that have enriched this article and improved its readability. Please find below reply addressing the reviewer's comment.

1. One small suggestion, when suggesting the DAA therapies as you have now added, I would advise it be listed as sofosbuvir and daclatasvir (Introduction, page 4). Currently you have added e.g. generic sofosbuvir Stand alone sofosbuvir should not be used to treat a genotype 3 population

Answer: We thank the reviewer for the valuable suggestion.

To address the reviewer's suggestion, we have now added daclatasvir to sofosbuvir as suggested by the reviewer (Introduction, page 4, second paragraph).