

## ESPS PEER-REVIEW REPORT

The authors would like to express their collective sincere appreciation to all three reviewers for their efforts and time spent reviewing our manuscript. We also express our thanks for all of the useful and valuable comments which have helped strengthen the manuscript. Below we provide a point by point specific response to each specific issue.

**Name of journal:** World Journal of Hepatology

**ESPS manuscript NO:** 21227

**Title:** The epidemiology of hepatitis C virus exposure in Egypt: Opportunities for prevention and evaluation,

**Reviewer's code:** 00506513 **Revisions to comments made by this reviewer are highlighted in yellow.**

**Reviewer's country:** Japan

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2015-07-06 18:14

**Date reviewed:** 2015-08-13 08:25

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

## COMMENTS TO AUTHORS

This review describes epidemiology and infection control of HCV in one country, Egypt. It is well organized review. The literatures, which are difficult to be available ones, are cited. These are helpful for readers. This is worth for publication in such open access journal. ?Table 1: References should be cited in each Exposure Route column to help for the readers. "IDU" should be fully spelled out. ?Table 2: "%" is missing in Prevalence column. ?Fig. 3 and 4: Explanatory notes in both vertical axis and horizontal axis are missing. ?Fig. 3 and 4 can be combined ?p. 15, 3rd paragraph, line 2: DHS should be defined by showing full spell. ?p. 15, 3rd paragraph, line 5: "Odds ratio =" is duplicated. ?p. 20, line 2: "anti-HC" is "anti-HCV". ?p. 20, Discussion, 2nd paragraph: It is difficult to

follow. This should be revised. ?p. 7, 2nd paragraph, line 3, and p. 22, 4th paragraph, line 7: “blood transfusion has 100% probability of transmission”: Reference(s) should be cited. ?References, especially journal names, should be described in accordance with author’s instructions of this journal.

**Response** [reviewer comments are reinstated and followed by our responses]

This review describes epidemiology and infection control of HCV in one country, Egypt. It is well organized review. The literatures, which are difficult to be available ones, are cited. These are helpful for readers. This is worth for publication in such open access journal.

?Table 1: References should be cited in each Exposure Route column to help for the readers. “IDU” should be fully spelled out. *Done*

?Table 2: “%” is missing in Prevalence column. ? *Done*

Fig. 3 and 4: Explanatory notes in both vertical axis and horizontal axis are missing. *Done*

?Fig. 3 and 4 can be combined –

>Actually these are entirely different graphs: the first shows the grouped frequency of injections by groups of 5, i.e. almost 70% those who received injections received 5 or less.

Figure 4 is unique data and original findings by the review on the relationship between the number of injections received and the percent prevalence of HCV, i.e. in those who received 20 injections HCV prevalence was 24.4%. Moreover this important graph shows a strong correlation coefficient (0.96) with increasing number of injections and increasing HCV % prevalence. This figure is essential to our review.

?p. 15, 3rd paragraph, line 2: DHS should be defined by showing full spell. *Done*

?p. 15, 3rd paragraph, line 5: “Odds ratio =” is duplicated. *Done*

?p. 20, line 2: “anti-HC” is “anti-HCV”. *Done*

?p. 20, Discussion, 2nd paragraph: It is difficult to follow. This should be revised. *Done*

?p. 7, 2nd paragraph, line 3, and p. 22, 4th paragraph, line 7: “blood transfusion has 100% probability of transmission”: Reference(s) should be cited. *Done*

?References, especially journal names, should be described in accordance with author’s instructions of this journal. *Done*



ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 21227
Title: The epidemiology of hepatitis C virus exposure in Egypt: Opportunities for prevention and evaluation,
Reviewer's code: 00504172
Reviewer's country: Italy
Science editor: Fang-Fang Ji
Date sent for review: 2015-07-06 18:14
Date reviewed: 2015-07-15 15:17

Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, SCIENTIFIC MISCONDUCT, CONCLUSION. It contains checkboxes for various evaluation criteria like 'Grade A: Excellent', 'Priority publishing', 'Google Search', etc.

COMMENTS TO AUTHORS

The review "The epidemiology of hepatitis C virus exposure in Egypt: Opportunities for prevention and evaluation" is very interesting and gives a fairly comprehensive overview of the situation in Egypt. The part on the epidemiology of HCV genotypes and their correlation with patterns of exposure (and the speculations on diffusion time of various HCV genotypes) is missing. It also would be interesting to describe the studies (if there are in Egypt) with the correlation, based on the sequencing of the viral genome, between index case and related infections following iatrogenic exposure. These topics could complete the review. Moreover there is a unclear point in page 19: " A statement in a summary of the findings reported a significant decrease from 2002 to 2004 in almost all indicators of infection control. It was concluded that infection control practices were extremely weak". It sounds a bit contradictory. It would be better to clarify.



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### Response:

The review “The epidemiology of hepatitis C virus exposure in Egypt: Opportunities for prevention and evaluation” is very interesting and gives a fairly comprehensive overview of the situation in Egypt. The part on the epidemiology of HCV genotypes and their correlation with patterns of exposure (and the speculations on diffusion time of various HCV genotypes) is missing.

>This is an interesting and complex comment. We did not include it. A justification for not including this issue is that it is not relevant to the contemporary iatrogenic transmission in Egypt which is well documented and which we have cited.

That said, we are unaware of any *heterogeneity* in exposure to HCV infection by genotype in Egypt. In Egypt, by far the most common HCV genotype is 4a. For example, data on the HCV genotype that may have been associated with HCV infection decades ago when there were ongoing PAT campaigns is not known, at least not directly. We have shown in a recent publication (51) that the role of the PAT campaigns in the larger HCV Egyptian epidemic may have been overstated relative to the even larger contemporary iatrogenic exposures in the large widespread health care system of the time. Perhaps most importantly, we are referring to the epidemiology of contemporary HCV exposure which is relevant to prevention.

It also would be interesting to describe the studies (if there are in Egypt) with the correlation, based on the sequencing of the viral genome, between index case and related infections following iatrogenic exposure.

>This is an interesting question, one that reflects on the role of so called “molecular epidemiology” (or for that matter epidemiology in which the infectious agent can be further classified and typed by one of several technologies such as serology or electrophoresis of polymorphisms as used in food borne outbreaks or sequencing) and if we understand the reviewer’s request, that is how HCV viral genome sequencing could be used to demonstrate infection between individuals. First, such studies have been challenging for a number of reasons not the least of which is due to very unstable HCV genome. This approach was tried to show transmission from mother to new born. In some cases the viral genome had mutated in the new born to the extent to be unmatchable to the mother. This has made the interpretation of these results problematic. The need for an index case of HCV to do this type of investigation is close to impossible. HCV rarely has a symptomatic onset needed find index cases which by definition have to be new cases. Moreover, if an index case was confirmed, there is a moral obligation to treat or refer to treatment.

We did cite [ref 33] which is essentially an anecdotal report using genomic sequencing to relate a family member to “new” HCV infection identified serologically overtime. The claim of intrafamilial transmission will always be tenuous given the very low or nonexistent transmission of HCV between monogamous discordant spouses.

We show that HCV is predominately iatrogenically transmitted in Egypt and should and can be prevented.



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We also show how to adapt epidemiologic methods to evaluate prevention efforts.

These topics could complete the review. Moreover there is an unclear point in page 19: “A statement in a summary of the findings reported a significant decrease from 2002 to 2004 in almost all indicators of infection control. It was concluded that infection control practices were extremely weak”. It sounds a bit contradictory. It would be better to clarify.

>Good point. We modified the statement to, “A statement in a summary of the findings reported a significant decrease from 2002 to 2004 in almost all indicators of infection control.” That is instead of an increase in infection control indicators, there was a decrease.



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## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**ESPS manuscript NO:** 21227

**Title:** The epidemiology of hepatitis C virus exposure in Egypt: Opportunities for prevention and evaluation,

**Reviewer's code:** 00506601

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2015-07-06 18:14

**Date reviewed:** 2015-09-01 01:39

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input checked="" type="checkbox"/> Major revision
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		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

This paper present a review of the epidemiology of the prevalence of HCV infection in Egypt. The paper present a view on how the Egyptian population, who has a high prevalence of infection, may be exposed to this virus. Specific comments: In the Abstract the authors state that due to a large body of literature on the iatrogenic exposures as the major driver of HCV transmission additional epidemiologic studies are not warranted. This is contradicted in one of the main references the authors use to make their case. Arafa et al. state that in adults especially those age 40-50 years the exposure to HCV was through schistosomiasis intravenous treatment that this population in rural Egypt were given as children. In children no iatrogenic factors were associated with an increase infection, suggesting a change in the pattern of HCV spread. If there is a changing pattern of HCV spread in the country, there should be new epidemiologic studies to detect new modes of spread. I worry that the authors have approached the problem of transmission of HCV in Egypt with a closed mind and are only trying to prove their case. The general population estimate is so high that it



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does not seem to make sense that all infection is iatrogenic since one would assume most people are healthy and not hospitalized. The only way this could happen is if all clinics vaccinated children with contaminated needles. Given that the one reference from the rural population in Egypt that demonstrates no iatrogenic transmission in children there is evidence at least in this one population that this is not happening. The figures do present increased prevalence in children compared to other developed countries so there are contradicting evidence. The authors dismiss IDU saying it poses a very low probability to the general population using a reference that does not even mention IDU. This makes me question their other references. I was surprised by the estimate on page 15 of the high rate of injections in Egypt at 281 million per year and that injections were administered by non-medical personnel such as housekeepers and relatives. The authors should expand on this to explain to readers who do not live in Egypt what these injections are and why they are being administered by non-medical people. It would help to explain what is happening in Egypt. One of the main questions I had was why are people in Egypt are having so many injections. The authors present the data and interpret this to mean that individuals have serious medical conditions. This has to be a rare event and not contribute to HCV prevalence on a population level. Millions of people in the country can't have serious medical conditions. The authors conclude the paper discouraging the continuation of population based studies but encourage facility based studies. Given their previous presentation that many injections are given in non-medical settings this does not make sense. I agree that there needs to be a change in the infection control culture in the country but it must be across the board in both the medical community and in the lay community that is involved in medical care. After this intervention evaluation especially among the children needs to be part of the prevention effort. Serosurveys along with infection control inspections which will be by necessity be periodic will be needed.

### Response:

This paper presents a review of the epidemiology of the prevalence of HCV infection in Egypt. The paper presents a view on how the Egyptian population, who has a high prevalence of infection, may be exposed to this virus. Specific comments: In the Abstract the authors state that due to a large body of literature on the iatrogenic exposures as the major driver of HCV transmission additional epidemiologic studies are not warranted.

This is contradicted in one of the main references the authors use to make their case. Arafa et al. state that in adults especially those age 40-50 years the exposure to HCV was through schistosomiasis intravenous treatment that this population in rural Egypt were given as children. In children no iatrogenic factors were associated with an increase infection, suggesting a change in the pattern of HCV spread. If there is a changing pattern of HCV spread in the country, there should be new epidemiologic studies to detect new modes of spread.

I worry that the authors have approached the problem of transmission of HCV in Egypt with a closed mind and are only trying to prove their case.

>A great deal of additional epidemiologic data has been published since data were collect by Arafa et al. in 2002 which solidly affirms the role of iatrogenic transmission. On page 3 of Arafa et al., the second

paragraph, “*Of all possible community-acquired risk factors, only cautery was found to be associated with an increased risk of infection (HCV antibody prevalence among exposed was  $4/23 = 17.4\%$ ;  $OR = 7.85$ ,  $95\% CI = 2.42, 25.4$ ), and remained significant on multivariate logistic regression analysis (Table 1).” Further on in the report, “*In those less than 20 years, the two independent risk factors (cautery and instrumental delivery) identified in the multivariate model ....*” It is our understanding that cautery and instrumental delivery are medical procedures and in this report, classified as iatrogenic exposures.*

There were other issues that need to be considered in order to make conclusions and interpretations from this report. Since the data collection in 2002, the overwhelming results of epidemiologic studies in Egypt have repeatedly identified iatrogenic exposure as the most significant route of infection in all age groups. Numerous newer reports, which include case control and prospective studies (Arafa et al. was cross sectional which limits the interpretation of associations and contemporary text books of epidemiology point out that cross sectional studies by design cannot confirm risk factors), have also shown that Egyptians of all ages are at risk of iatrogenic exposures. In addition, the collective global literature on HCV transmission firmly establishes this virus as a blood borne pathogen with well-defined routes of transmission.

The general population estimate is so high that it does not seem to make sense that all infection is iatrogenic since one would assume most people are healthy and not hospitalized.

>We do not suggest in this manuscript that iatrogenic exposures occur only in hospitals. Many injections are given in home settings usually by untrained providers or at pharmacies. A large number of persons visit dental clinics either in governmental hospitals or private practice. As reported and pointed out in our review, many of these clinics lack the proper infection control measures. These and other common and simple procedures are considered possible exposures to HCV infection without implying that most people are unhealthy to the point of needing to be hospitalized.

The only way this could happen is if all clinics vaccinated children with contaminated needles.

> We do not make a claim that all clinics vaccinate children with contaminated needles. Moreover, needles are only one source of iatrogenic exposures.

Given that the one reference [Arafa] from the rural population in Egypt that demonstrates no iatrogenic transmission in children there is evidence at least in this one population that this is not happening.

>The observations by Arafa et al can also be explained by bias. Iatrogenic exposures based on historical information from children or indirectly from their parents is considered by most epidemiologists as unreliable. This is technically known as recall bias which can operate in either direction, i.e. lack of sensitive and or lack of specificity.

The figures do present increased prevalence in children compared to other developed countries so there are contradicting evidence.

The authors dismiss IDU saying it poses a very low probability to the general population using a reference that

does not even mention IDU.

>We quote from the abstract in that reference, "In most countries, prevalence rates were higher among males, reflecting higher rates of injection drug use."

This makes me question their other references. I was surprised by the estimate on page 15 of the high rate of injections in Egypt at 281 million per year and that injections were administered by non-medical personnel such as housekeepers and relatives.

> We reported the findings correctly. The rate of injections in Egypt have been reported in several studies. All are consistent with these rates. This is also consistent with our own anecdotal observations in Egypt.

The authors should expand on this to explain to readers who do not live in Egypt what these injections are and why they are being administered by non-medical people. It would help to explain what is happening in Egypt.

>We welcome readers to follow up by reading the studies cited in the references for their own understanding.

One of the main questions I had was why are people in Egypt are having so many injections. The authors present the data *and interpret* this to mean that individuals have serious medical conditions.

>We can only assume you mean the authors of the studies on injection rates. We have not made such interpretations.

This has to be a rare event and not contribute to HCV prevalence on a population level. Millions of people in the country can't have serious medical conditions.

>We welcome your attention to the literature cited and indeed abundant additional literature on this subject that we did not cite.

The authors conclude the paper discouraging the continuation of population based studies but encourage facility based studies.

Given their previous presentation that many injections are given in non-medical settings this does not make sense.

>Our review of the epidemiologic literature on HCV in Egypt directs us not to recommend continued epidemiologic investigations on patterns and determinants of HCV infection. That has been done. Specific facility based studies have not been recommended by this review. The results of our review is that studies on the epidemiology of exposure to HCV infection in Egypt are very limited. Such data are essential to design effective interventions and in turn to evaluate those interventions.

I agree that there needs to be a change in the infection control culture in the country but it must be across the board in both the medical community and in the lay community that is involved in medical care.

After this intervention evaluation especially among the children needs to be part of the prevention effort.

Serosurveys along with infection control inspections which will be by necessity be periodic will be needed.



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>There are other public health, economic, social (HCV stigma) as well as moral and ethical issues that cannot be justified for continued testing of Egyptians for HCV given the information and tools that are available that can prevent transmission of HCV. Limited resources and funds have to be directed at prevention. Most importantly, the epidemiology for the evaluation of HCV public health interventions is very different. Some readers who are not familiar with the evaluation of public health interventions and may not know that linking health outcomes, for example incidence, has too often been found too costly and too complex to do. This is especially true for HCV which does not have a unique and specific acute phase of infection and more often does not have an acute phase at all.

In a public health intervention the focus has to be on eliminating the exposure and the distributions and determinates of exposure i.e. epidemiology of exposure to HCV or the epidemiology of HCV E.