Author’s response to reviews

Title: Why all blood donations should be tested for hepatitis E virus (HEV)

Authors:

Joachim Denner (DennerJ@rki.de)
Sven Pischke (s.pischke@uke.de)
Eike Steinmann (eike.steinmann@ruhr-uni-bochum.de)
Johannes Blümel (Johannes.Bluemel@pei.de)
Dieter Glebe (Dieter.Glebe@viro.med.uni-giessen.de)

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Author’s response to reviews:

Dear Madam, dear Sir,

please find enclosed the formatting changes.

We included email addresses of all authors in title page
Reformatted Abstract section based on the article type
Provided Declarations section Header, Reformat Declaration section based on the article type
Included all of the authors in A.C. and state their role on the study.

With best regards

Joachim Denner

Anders Boyd

BMC Infectious Diseases

https://bmcinfectdis.biomedcentral.com/
Dear Dr. Boyd,

Please find enclosed the revised version of our manuscript “Why all blood donations should be tested for hepatitis E virus (HEV)” by Joachim Denner; Sven Pischke; Eike Steinmann; Johannes Blümel; and Dieter Glebe, submitted to BMC Infectious Diseases (INFD-D-19-00441).

Please find also enclosed below the point-by-point answers to the reviewers. We would like to thank them for suggestions helping to improve our manuscript.

With best regards

Joachim Denner

Reviewer 1

Hepatitis E virus (HEV) of genotype 3, is now widely accepted to affect people in industrialized nations. While most affected healthy individuals have an asymptomatic infection, infection of immunocompromised people can lead to chronic infection which may cause liver fibrosis and cirrhosis. Moreover, patients with underlying liver disease can develop acute-on-chronic liver failure and have a high mortality rate. HEV infections are usually caused by consumption of undercooked meat products mainly originating from swine or by contact with pigs, however, several cases of HEV transmission via blood transfusions have been described. While some countries have started selective HEV RNA screening of blood products used for especially vulnerable patients, other countries have started universal screening of blood products. In this manuscript the authors conclude that all blood donations should be tested for HEV RNA. The manuscript gives a thorough introduction to HEV biology and epidemiology before emphasizing the need for HEV testing of blood products.

Minor points:

Comment 1

1. Abstract line 32-34: "HEV-3 and HEV-4 are widely distributed in pigs and can be transmitted to humans by undercooked meat, contact with pigs and also by blood transfusion." Since also other sources of HEV are found, as stated later in the manuscript, please include a mainly ("...transmitted to humans mainly by..."). The same is the case for line 33 under the heading "HEV-Biology and prevalence".
Answer 1

Thank you for this important hint, the text was changed accordingly in both cases.

Comment 2

2. Heading "Background" line 10-11. According to Euro Surveill. 2018 Aug;23(35). doi: 10.2807/1560-7917.ES.2018.23.35.1700616, Switzerland also planned to start screening of all blood products from November 2018. Please include this information.

Answer 2

Thank you, this information was included.

Comment 4

3. Heading "HEV-Biology and prevalence" line 30. "...HEV-7 was found in a dromedary camels...". HEV-7 was also found in a liver transplanted patient regularly consuming camel meat and milk. Please include this information and the reference for this (Lee et al. 2016. Gastroenterology 150(2):355-7.e3. doi: 10.1053/j.gastro.2015.10.048.).

Answer 4

Thank you, for unknown reason this information disappeared from my previous manuscript. It was introduced again.

Comment 5

4. Heading "Transmission of HEV-3..."Line 4-18. Other studies in these countries and Spain showed a prevalence between 1:1250 to 1:9500 [33-35]. I guess this sentence is about the HEV RNA prevalence and not the HEV IgG prevalence, as described in the sentence above and below? Please make sure that this is well described in every sentence of this paragraph.

Answer 5

In order to make clear whether the prevalence is based on HEV RNA or IgG measurement, we introduced a table showing all results:
Table 1 HEV seroprevalence and viremia in blood donors in Western countries

<table>
<thead>
<tr>
<th>Country</th>
<th>HEV IgG positive (%)</th>
<th>RNA positive</th>
<th>Reference</th>
<th>Year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>29.5</td>
<td>1:1200</td>
<td>26</td>
<td>2012</td>
</tr>
<tr>
<td>France</td>
<td>22.4</td>
<td>1:2218</td>
<td>27, 28</td>
<td>2014, 2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:744</td>
<td>29</td>
<td>2017</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>27.0</td>
<td>1:2671</td>
<td>30</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:600</td>
<td>31</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.600</td>
<td>31</td>
<td>2015</td>
</tr>
<tr>
<td>England</td>
<td>12.0</td>
<td>1:2848</td>
<td>32</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:7000</td>
<td>33</td>
<td>2012</td>
</tr>
<tr>
<td>Scotland</td>
<td>4.7</td>
<td>1:14520</td>
<td>34</td>
<td>2013</td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td>1:2330</td>
<td>35</td>
<td>2016</td>
</tr>
<tr>
<td>Spain</td>
<td>19.9</td>
<td>1:3333</td>
<td>36</td>
<td>2015</td>
</tr>
</tbody>
</table>

5. Heading "Transmission of HEV-3..."Line 24."... seems to depend upon the virus load [30, 43]." According to the study by Hewitt et al 2014 (Lancet. 384(9956):1766-73. doi: 10.1016/S0140-6736(14)61034-5), transmission also depends on the blood component given. Please include this information.

Answer 6

Thank you for this important remark, this information was included.

Reviewer 2

The focus in this debate is the transmission of HEV-3 by blood transfusion. Authors listed the harm of HEV-3 and arguments in favor of testing all blood donations for HEV-3 to prevent transmission were summarized. The ideas are interesting and may provide more suggestions for the prevention and control of hepatitis E in the real world. Also, there are some problems needed to revise or clarify.

Comment 1

1. Page 2.line 12 may delete "1."
Comment 2

2. Page 2.line 48 "Blood testing" may be added into keywords.

Answer 2

Blood testing was added to the keywords.

Comment 3

3. Page 3.line 57 "found in wild boars [114-16]" may change to "found in wild boars [14-16]."

Answer 3

Sorry for the mistake, it was changed.

Comment 4

4. Page 5.line 36 "under circumstances requiring blood or plasma transfusion. [52, 53, 63, 64]" may delete the "." after the "plasma transfusion".

Answer 4

Thank you, was deleted.

Comment 5

5. Page 5.line 36-39 "Third, the handling of two separate types of blood donations would increase logistical cost and may even lead to product losses due to the stockpiling of tested and non-tested donations." It is not easy to understand that why "lead to product losses due to the stockpiling of tested and non-tested donations"? This needs more examples to explain.

Answer 5

For example, in the case more tested material is required, stored non-tested material will not be used and may expire and vice versa.

Comment 6

6. My suggestion is to increase the discussion of screening strategy evaluation, such as literature 61, from the perspective of health economics to illustrate the cost-effectiveness of screening for hepatitis E in blood donors.
Answer 6

Following the advice of the reviewer, we extended the discussion:

Analysing the cost-effectiveness of the screening of blood donations for HEV in the Netherlands, the authors came to the conclusion that preventing HEV transmission by screening of blood donations appears not excessively expensive compared to other blood screening measures [61]. However, since only a small number of HEV infections are due to blood transfusions, the overall impact on HEV disease.