

ANSWERING REVIEWERS



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6913-review.doc).

Title: Genetic diversity of hepatitis B virus lineages in human and nonhuman hosts: potential for bidirectional cross-species transmission

Title was changed to "Hepatitis B virus lineages in mammalian hosts: potential for bidirectional cross-species transmission"

Author: Cibele R. Bonvicino, Miguel A. Moreira, Marcelo A. Soares

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6913

The manuscript has been improved according to the suggestions of reviewers:

(1) Format has been updated

The title was changed and is in accord to BPG's Revision Policies (Title should be less than 12 words).

A "Core Tip" was added to the manuscript.

(2) Revision has been made according to the suggestions of the reviewers

Reviewed by 02455686

1. What was the search strategy used to capture the papers cited in this review? In which databases was it conducted? What were the inclusion/exclusion criteria for papers? Were any papers captured excluded, and if so, how many, and why?

It is important to emphasize that our review did not intend to be comprehensive or systematic and therefore to approach all available literature in the field. Our review is however, to the best of our knowledge, the first and only to address current information regarding the impact of infection of nonhuman mammalian hosts by HBV-related viruses. For retrieving the articles cited in the present review, we have searched PubMed and Google using the terms "Hepatitis B virus" OR "HBV" AND "primate" OR "rodent" OR "bat" OR "chimpanzee" OR "gorilla" OR "orangutang" OR "rhesus" OR "New World primate" OR "neotropical primate" OR "nonhuman". Only articles in English were considered, so those in other languages were excluded from the review. In addition, for papers showing duplicate information regarding HBV-like infections of hosts, only the oldest (original)

description was kept.

2. *In the section on infection in Old World primates, you state 'Strong phylogenetic associations of chHBV with chimpanzee subspecies and their geographic distribution have been found'. (Page and line numbers would be helpful!) How do you define a strong phylogenetic association?*

We changed the text "Strong phylogenetic associations of chHBV with chimpanzee subspecies and their geographic distribution have been found" for "Strong associations between chHBV strains and their host geographic distribution have been found".

As per the Reviewer's suggestion, we have added line numbers to the revised version of the manuscript.

2. *Further in the paragraph you state that chimpanzees constitute putative reservoirs of infectious agents. To support this statement, an estimate of prevalence of infection would be very helpful.*

In the second column of Table 1, the prevalence of HBV infection in chimpanzees is shown for some studies. We have referred to data from that Table in a new sentence following the one cited by the Reviewer in the revised manuscript ("High prevalence rates of chHBV, of up to 25% in some wild communities (Table 1), further enhances the risk of cross-species transmission events").

Reviewed by 02539179

1. *While comprehensive evidence of HBV-like infection in nonhuman mammals were listed and discussed, the potential importance of these infection on the HBV infection in human being were not well highlighted. The WJG readers must be more interested in whether other hepatitis virus strains or growing strains from nonhuman mammals would induce hepatitis B in human being, or whether non-human mammals can be infected by human hepatitis B virus, thus they may serve as hepatitis B models.*

Several instances of references to the potential that non-human mammals can be infected by human hepatitis B virus can be found in the manuscript, including the following excerpts:

"An interesting case was reported by Tatematsu et al. [13], showing that the new human genotype J found in one patient resulted from a recombination event between human HBV/C and a gibbon HBV." (line 262)

"Dupinay et al. [54] detected the presence of the human HBV sub-genotype D3 in serum and liver samples of *Macaca fascicularis* from the Mauritius Islands. An HBV DNA prevalence of 25% in serum samples of 120 specimens and 42% of liver samples from 50 specimens was reported." (line 291)

"*Papio ursinus* liver samples from specimens caught in South Africa were found to be naturally infected with HBV DNA subgenotype A2, with evidence of lifelong persistence of this virus and occurrence of occult HBV infections." (line 285)

"Recently, serological data from several samples from swine from Brazil and partial genome sequencing (252-365 bp) of three of these samples confirmed HBV infection, with sequences sharing 93-96% of identity with human HBV[60]." (line 337)

2. *Transmission pathways should also be discussed, as it is well known that HBV spreads through blood and other body liquids.*

We have added those issues at the Concluding remarks part of the manuscript.

3. The manuscript must be shorten in great effort to fit the scope and the requirement of WJG, and have to be more disease-related.

We reduced approximately 10% of the body of the manuscript (excluding abstract and core tip), mostly by deleting the descriptions of the species' geographic distribution that are already contemplated in Figure 1.

(3) References and typesetting were corrected

The format of the references was revised and now is in accord to BPG's Revision Policies.

Sincerely yours,

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