

This is a Response Letter to the Reviewers' Comments to Manuscript no. 26033

Answers to Reviewer 02528327's Comments

Comment no. 1

The quality of the review could be improved by including a general overview of HBV (introducing the diagnostic relevant HBV markers), and the general HBV situation in Indonesia in the Introduction section. The presence of the predominant HBV genotypes in Indonesia should be included in the Introduction section, and not introduced in the section "HBV among hemodialysis patients". Then the individual paragraphs can build on the general information presented in the Introduction section. Similarly, HBV markers such as HBe antigen should be introduced in the Introduction section, and not in the section of the "Immunization program and its impact".

Answer:

Introduction section has been revised according to the reviewer's suggestion.

Comment no 2

Figure 1 provides the prevalence of HBsAg positive individuals for certain provinces. Please clarify whether the provided number is the average number across all age groups, and therefore including the individuals born before and after the introduction of the immunization program. Please clarify, for the provinces without the prevalence number, are there no data available or published?

Answer:

The reviewer is correct: the provided number in Figure 1 is the average number across all age groups, and therefore including the individuals born before and after the introduction of the immunization program. The population were those with more than 1 year of age (general population) in 2007, after 10 years of implementation of National HepB Immunization. The information for age has been added in the legend of the Figure 1. For the provinces without the prevalence number, there are no available data.

Comment no. 3

Page 5: The four provinces implementing a routine HBV immunization in 1991, are these the provinces with a lower HBV prevalence (as shown in Fig. 1)?

Answer:

In 2007, the HBsAg-positive prevalence in the four provinces (West Nusa Tenggara, Bali, Yogyakarta and 5 districts in East Java) varied (2.49-10.11%).

Comment no. 4

Please can you specify the provinces (4 provinces, 6 other provinces, in seven of its provinces).

Answer:

The names of four provinces and 6 other provinces have already completed in the revised manuscript. But the names of seven provinces were not mentioned in the cited original reference.

Comment no. 5

Page 6: "HBV infection has been reduced by the universal newborn HepB immunization program": please show tables to contrast the impact, HBV prevalence in individuals born before and after the introduction of the vaccine program, then present situation specific for pregnant women, and specific groups of the society. Please provide some summarised data (maybe in Table form) for age groups born before or after the introduction of the immunization program.

Comment no. 6

The text is very descriptive, with many numbers. As mentioned in comment 5, include tables, and be concise in the text (summarise).

Answer for Comments no. 5 and 6 :

Table 1 has already showed the prevalence of HBsAg positive in some age groups population in Indonesia, in 2007 and 2012. It means that in 2007, the >10-year-old children were born before National HepB Immunization Program (since 1997-2000) and <10-year-old children were born after National HepB Immunization Program.

The >10-year-old children had higher HBsAg-positive rate than that of <10-year-old children. In 2012, there were decline HBsAg-positive rates in children with 1-5 year of age and 6-12 year of age, compared with those in 2007. The table showed the lower HBsAg-positive rates after implementation of National HepB immunization.

Due to very limited data on HBsAg prevalence in pregnant women, it was only mentioned in the text.

Comment no. 7

Please provide a reference for a HB-Uniject vaccine.

Answer:

We added it in the manuscript (reference no. 17).

Comment no. 8

Page 8: The authors listed some identified substitutions, which are most likely associated with genotype specific variations. Any data published regarding the G145R mutation in Indonesia? G145R seems to be a true vaccine escape mutant (e.g. Amini-Bavil-Olyae, et al. 2010, J Virol. 84: 1026-33).

Answer:

G145R mutation in Indonesia has been reported by Yamani et al (J Clin Microbiol 2015; 53: 3165–3175) in one patient with advanced liver disease. Study about G145R mutation has not been yet reported in vaccinated children in Indonesia.

Comment no. 9

page 9: “ Variation in the major hydrophobic region was ...” - should read “hydrophilic”

Answer:

Thank you; it has been corrected in the manuscript.

Comment no. 10

Page 10: "The risk of HBV transmission from blood-contaminated itemsgreater and more serious than ..." Please give reference for this statement.

Answer:

It could be found in part, in reference no. 66 (Edey et al., 2010). Other part is my and other opinions. The logic is, HBsAg-positive blood may have a very high load of virion, and the virus can survive on environmental surfaces for more than 1 week in dried blood. Infectious HBV virions have also been demonstrated on environmental surfaces in the dialysis facility in the absence of visible blood patients with Chronic Kidney Disease (CKD), and patients with CKD tend to become life-long carriers of HBV if infected.

Comment no. 11

Page 11: "Our previous study in Surabaya showed prevalence of anti-HCV, while recent study ... showed ... prevalence of hepatitis B infections ..." What's the link between a previous study on HCV and the recent study on hepatitis B? Context unclear.

Answer:

Our previous study also showed that hemodialysis duration and the number of blood transfusions were significantly associated with HCV infection but not with HBV infection. This is one of the proofs that the causative is nosocomial transmission, since patients with hepatitis B but not hepatitis C were isolated in separate rooms. We need to read all sentences in the paragraph as a whole to understand my explanation above.

Comment no. 12

Pages 12 and 13: "Malay ethnic group, the main ethnic group in Indonesia ..." versus "largest ethnic group in Indonesia is the Javanese" Please clarify.

Answer:

Thank you. We corrected “Malay” into “Javanese”. In this study, Malay means Javanese.

Comment no. 13

page 13: Reduce the section HLA type and its association with pulmonary tuberculosis, *H. pylori* in Indonesia; this is not the topic of the review. The background information of chronic hepatitis B and its association to genetic markers in Asian countries is valuable. One publication (Png et al. 2011) has investigated the association of genetic markers and immunization outcomes in an Indonesian population. Host genetics and HBV infections seem to be very limited, and not investigated for the Indonesian population; therefore expand on the Asian background information and the published study, Png et al 2011.

Answer:

We agree with the reviewer’s comment. We deleted the sentences mentioning tuberculosis, leprosy and HP infection. In addition, we added the sentences and references and discussed deeply based on the Indonesian study.

Comment no. 14

Have been any studies performed with Indonesian patients regarding IL28B (interferon lambda 3) polymorphism and HBV? Kim SU, et al., 2013. Plos One 8(7): e69166).

Answer:

Thank you for suggestion. As reviewer pointed out, IL28B SNP is an important genetic factor for HBV infection. So far, no study was found regarding IL28B polymorphism and HBV infection in Indonesian population. Based on the reviewer’s comment, we added the sentences references containing the relationship between IL28B SNP and HBV infection.

Comment no. 15

abbreviation “SNP” not introduced.

Answer:

Thank you; it has been corrected in the manuscript.

Comment no. 16

Reference Beasley RP, NOT Beasly

Answer:

Thank you. It has been corrected in the manuscript

Comment no. 17

Reference 41 unpublished.

Answer:

When we submitted the manuscript, this reference was not accepted in a journal yet. Now, it is accepted already in a journal. We corrected reference 41 in the manuscript as “in press”

Comment no. 18

No first name provided in publications J Med Virol and Virus Res for first author Mulyanto. Remove initials “SN” or “P”. Check author list, second author (Virus Res) Pancawardani, P. second author (J Med Virol) Depamede, SN.

Answer:

Thank you for the accuracy. They have been corrected in the reference list in the manuscript.

Answers to Reviewer 00504271’s Comments

The manuscript has two Figure 1, and the second figure 1 should be removed.

Answer:

In Guidelines for Manuscript Preparation, it is mentioned that figures with labels, arrows or other markers, photographs, clinical images, photomicrographs, gel

electrophoresis, and the like that include labels, arrows or other markers must be submitted in 2 versions: one version with the markers; and the other without.

Figure 1 needs its legend. What do numbers in the map indicate ?

Answer:

Thank you for the accuracy. It is revised now. The numbers indicate the prevalence of HBsAg positive among people more than 1 year of age in their appointed regions.

Answers to reviewer 01804246's comments

This is an interesting paper. Maybe it is a little too long and very heterogeneous, mixing newborns, with chronic hemodialyzed patients and genotypes. Some points are speculative (in HDV patients). In conclusion maybe not genetic, but the transmission between patients is the cause for quite high prevalence of viral chronic infection.

Answer:

In this Review Paper of The current HBV infection situation in Indonesia and its genetic diversity, we would like to present an update data of HBV infection in Indonesia, a populous- multi ethnics- developing country, with several problems of HBV infection in several groups of communities, such as children born to infected mothers, high risks groups of hemodialysis, OBI. The various ethnic groups impact on the various geno/subgenotypes, as well as the host genomes do.

Reviewer mentioned HDV, possibly means hemodialysis (HD). In the HD study it was found that all patients belonged to HBV subgenotype B3, which is the most common one among Javanese in the general population in the same area of the study. Previous studies showed unique subgenotypes in other ethnics and geographic regions of Indonesia, in the general population. Based on those previous results, we presume that HBV among HD patients in those area would present a unique and different HBV subgenotypes from that of Javanese in Java.

We agree with the reviewer that the transmission between patients is the cause for quite high prevalence of viral chronic infection.

Answers to Reviewer 00012051's Comments

Some minor points could be improved: A table to compile the genotype results may be more precise and descriptive.

Answer:

HBV genotypes in the general population in Indonesia have been presented in a review paper recently. In this manuscript we focus that in the hemodialysis patients, which the result is not varied. That is why we do not make a table.

Also a table to summarize the HLA types and susceptibility One point is unclear is the compilation of OBI with Pre S mutants, these are 2 different problems, OBI can be due to "a determinant" mutation but not to pre S mutant that also are important but should be considered separately Also some important references on OBI are missing

Answer:

Thank you for reviewer's comment. According to the suggestion, we arranged the sentences and made a table to understand easily (Table 2). In addition, we agreed that OBI detected not only escape mutant and added several important articles about OBI. The section of "Variation in Pre-S/S region" was separated from "Occult HBV infection".

Answer to Reviewer 03479132's Comment

This is a review article that discusses certain aspects of the current state of hepatitis B virus infection in Indonesia. It is of relevance to the journal's readers in Eastern Asia.

Answer:

No answer is needed. Thank you

Answers to editor

Please provide the approved grant application form(s) or funding agency copy of any approval document(s)/letter(s). A copy of the full approved grant application form(s), consisting of the information section and body section, should be provided to the BPG in **PDF** format. Thank you

Answer:

Actually for this Review manuscript, there is no grant from any agency. What I meant was, several main sources of references are from our papers that were supported by Ministry of Research, Technology and Higher Education, Republic of Indonesia.

So, now I decide to delete the agency as Supporter.

A copy of signed statement should be provided to the BPG in **PDF** format, **which are necessary for final acceptance**, Thank you!

Answer: Such statement has already been provided. Please find attached. Thank you.

Audio core tip:

In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

Answer: The Audio core tip is prepared. Please find attached.

For those references that have not been indexed by PubMed, a printed copy of the first page of the full references should be submitted.

Answer:

First page of the full reference of those references are attached.