

Response letter

Reviewer's code: 00053786

Reviewer's comment: Aneley Getahun as presented a concise, well-written manuscript concerning the prevalence of HBsAg among a cohort of prenatal women from the Solomon Islands. A high endemicity was reported using a rapid test validated by ELISA. All sections are clear and the results well discussed. I suggest that the author add a little more information regarding the burden of disease derived from HBV-related disease such as cirrhosis and hepatocellular carcinoma, and if the genotypes are the same as in other regions of the Pacific. I find the results academically interesting given the fact the HBV infection is highly endemic in several indigenous populations worldwide that may be unexplored. On the hand, I find it alarming that the human population is still at risk for HBV infection. This study reports significant information that impacts world health. Thus, efforts to eradicate HBV infection worldwide should begin by considering regions of the world like the one reported herein. Human and technological resources should be provided to aid in lowering the prevalence rate in these populations. Congratulations to the author!

Author's response: We have incorporated information regarding serotypes as well as complications of HBV infection in Solomon Islands and the Pacific. This is found on page 6-7 of the revised manuscript and it reads as follows:

HBV C3 and D4 are the two prevalent subgenotypes in Solomon Islands and in the Pacific region [13-16]. Utsumi *et al.*, [13] further reported genotype to be specific with ethnicity where genotype was C were predominant in Melanesians while genotype was D was common among Micronesians. However, this study was not designed to further evaluate the genotype distribution as it was a simple prevalence study. Further studies to examine this are under consideration pending funding and partnerships.

There is paucity of information on the prevalence of complications of HBV infection

such as cirrhosis and primary hepatocellular carcinoma in Solomon Islands. This is partly due to the local challenges related to availability of clinical services as well as linkage to data capture with various disease notifications, this is also worthy of addressing and is being considered as part of an overall program development to support hepatitis services in Solomon islands. Historically, the island reported a high incidence of liver cancer among males ^[17]. According to the 2014 WHO report, liver cancer was the single most common cause of cancer in males ^[18]. Mortality from HBV related complications in Solomon Island remains unknown. Hepatocellular carcinoma is common in neighboring Melanesian islands of Fiji ^[19] and Vanuatu ^[20].

Reviewer's code: 00504673

Reviewer's comment: This study is providing HBsAg seroprevalence among randomly selected pregnant women (n=240) in Honiara, Soloman Islands. It is a cross sectional study showing high HBsAg rate(13.8%) in the studied population which is similar to the previous similar study dates back to 2008. The study design, material-methods are appropriate for the aim. The results are typical for a HBV endemic population but somewhat limited. It would have been more interesting if anti-HBs and anti-HBc total results of the study group were also provided. I believe the impact of the study is limited on the audience of the journal.

Author's response: We agree with the reviewer comments and it would have been ideal to undertake such a study to document this more fully. However, studies in resource poor settings face many challenges including resources access. Given the limitation in funds, we feel that we have contributed significantly to the current understanding of the burden of disease and increase in need to address this need. Further, subsequent advocacy and awareness will hopefully lead to the suggested type of studies. The determination of anti-HBs and anti-HBc remain outside the scope of our study. However the team has assessed the prevalence of HBeAg among the 33 study participants with positive HBsAg. This has enabled the team to evaluate infectivity and

the risk for vertical transmission of HBV to infants. Detailed description of the laboratory testing methods, results and discussion are on page 8, 11 and 13-14, respectively. Below is the excerpt from the revised manuscript:

Materials and methods

From the 33 positive samples for HBsAg, 30 samples were analyzed for HBeAg using the ABON HBV combo test kit [ABON Biopharm, Hangzhou Co., Ltd]. The remaining 3 samples were insufficient for further testing. The testing procedure and interpretation was carried out according to the manufacturer's instructions. Positive results were indicated by two red bands; one in the test region and other in the control region. Negative results were indicated by one red band on the control region.

Results

Of the 33 HBsAg positive pregnant women, 30 were tested for HBeAg. The overall prevalence of HBeAg was 36.7%. Higher prevalence was recorded among women between 20-24 years old (54.5%) followed by 25-29 years old (27.3%). All the HBeAg positive women were from Melanesian ethnic group and 54.5% reside in urban areas.

Discussion

Our study for the first time reports the prevalence of HBeAg among pregnant women in Solomon Islands. The overall prevalence of 36.7% is comparable to the rates reported among mothers and the general population. Furusyo *et al.*, [10] reported an overall prevalence of 41.3% among 315 HBsAg positive adult patients attending general outpatients and blood donors. The prevalence did not differ by sex however patients from Melanesian ethnic groups had significantly higher HBeAg seropositive compared to the other two ethnic groups. Another study among mothers of children who received vaccination reported HBeAg prevalence of 40.7% [26]. Subsequently in 2001, seroprevalence of 35% was reported among 206 blood donors with chronic hepatitis [14]. All studies reported a progressive decline in HBeAg sero-prevalence with increasing age.

Wilson *et al.*, [27], reported high prevalence of HBeAg among pregnant women in the Pacific region which ranged from 48% in Kiribati to 70% in Fiji. Hepatitis B e antigen determines infectivity. High prevalence of HBe antigen in pregnant women coupled with low up take of birth dose vaccine in Solomon Island increase the risk for vertical transmission of HBV to their newborns.

Reviewer's code: 00506525

Reviewers comment: If possible, update references to 2016

Author's response: The team has actively searched for studies published in 2015 and 2016 from the Pacific Island Countries. Relevant recent publications have been added to the reference section.

Response to Journal Editor-in-Chief (Associate Editor) comments

Comment #1 - In agreement with one reviewer the reference/literature list should be updated. There are number of citations from the late 1990 years. I am sure that there are newer reports available. So, please correct this.

Authors' response: The reference section has been revised. In the updated manuscript, there are only three references from the 90s. Ref #10 and 11 are seroprevalence studies among the general population and blood donors in Solomon Islands and Ref # 17 is the only historical data on liver cancer in the island.

Comment #2 In accordance to another reviewer comment the reports of Utsumi et al Int J Mol Med. 2011;27(6):829-34; Furusyo et al. Am J Trop Med Hyg. 2004;70(5):571-5 should be discussed.

Authors' response: The findings of the above two reports have been described in the introduction and discussion sections. In the revised manuscript we incorporated more information including, relationship between genotypes and HBeAg, anti HBe , demography and biological factors as well as severity of disease (page 7&8). In addition a description of study participants and the HBeAg findings (by age and ethnicity) are reported in the discussion section (page 13&14)

HBV C3 and D4 are the two prevalent subgenotypes in Solomon Islands and in the Pacific region^[13-16], Utsumi *et al*^[13], further reported genotype to be specific with ethnicity where genotype was C were predominant in Melanesians while genotype was D was common among Micronesians. The prevalence of HBeAg was higher among carrier of HBV subtype C compared to carriers of subtype B however it was not statistically significant. In this study there was no statistically significant difference between carriers of the two genotypes in terms of sex, liver function test (AST, serum

albumin and total bilirubin) and anti-HBe seroprevalence. Previous study in Solomon Islands reported significantly higher prevalence of HBeAg among carriers of genotype C which could be associated with severe hepatic inflammation and complications [14]. However, these studies were not designed to further evaluate the relationship between genotype and clinical progression as they were cross-sectional prevalence studies.

Comment # 3 - If possible also from the budget, anti-HBs and anti-HBc tests could be included.

Authors' response: We acknowledge potentially helpful information would be gained with the addition of surface antibody and core antibody. However, the current study addresses the prevalence of chronic infection in this cohort. It is expected that high rates of core and surface antibody levels will be found. To accurately assess this, we will need to send samples for immunoassay to a laboratory outside of the Pacific Islands with associated additional cost. At this stage, this is outside of the scope of this study.

The resources to do these assays are currently not easily accessible, nor is there adequate funding. We will continue to explore avenues to continue to contribute to increased understanding of this disease.

Comment # 4 - Clinical data and especially from the course of hepatitis B from the pregnant could be added to the study, which will enhance the impact of the report.

Authors' response: The team has incorporated concise information on the clinical course of chronic hepatitis B infection in pregnancy, its complication and pregnancy outcome in the introduction section (page 8).

The clinical course of chronic HBV infection generally does not change during pregnancy and chronic infection is not implicated in increased maternal morbidity or mortality [21, 22]. Most pregnant women with chronic HBV infection are asymptomatic and often detected

during routine ANC screening. Pregnancy related complications and perinatal outcomes of chronic HBV are not well elucidated. Some studies reported gestational diabetic, antepartum hemorrhage, preterm labour and lower Apgar score to be associated with chronic infection [23, 24]. Recent large scale studies from the US and China revealed no association between maternal HBV infection and the risk of fetal growth retardation, pregnancy induced hypertension or preeclampsia [24, 25]. In Solomon Islands, the impact of chronic HBV infection on pregnancy outcomes has not been investigated.

Specific to this cohort, the clinical outcome of patients who have been found to be positive is critical to their care and we hope to undertake a second part of the study to explore this further and provide linkage to care. This is currently under consideration and in discussion with the Ministry of Health. We hope to be able to provide this data at a later point as part of a longitudinal study and are grateful for the suggestion.