Author's response to reviews

Title: Determinants of suboptimal hepatitis B vaccine uptake among men in the Republic of Korea: Where should our efforts be focused: Results from cross-sectional study

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Author's response to reviews: see over
Editor-in-Chief

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Editor-in-Chief:

Thank you very much for your e-mail containing reviews of January 14, 2013. We are pleased to hear that our manuscript “Determinants of suboptimal hepatitis B vaccine uptake among men in the Republic of Korea: Where should our efforts be focused: Results from cross-sectional study (MS: 1712246983721118)” will be accepted for publication if appropriately revised. We are submitting the revised manuscript, on which we indicated where we made changes in response to suggestions of two reviewers in yellow and a point-by-point response to reviewers’ comments.

I guarantee that this or similar material has not been and will not be submitted by me or my colleagues to any other publication prior to its appearance in the BMC Infectious Diseases, and that all of my co-authors have made a substantive and specific intellectual contribution to the article.

We wish to thank you and the reviewers for the valuable comments and helpful suggestions which contributed significantly to the revision of our manuscript.
With regards,

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Point-to-Point Responses to the Reviewers’ Comments

Thank you for the valuable comments.

We revised the paper in accordance with the reviewers’ comments, and the revisions are summarized below and highlighted in the manuscript.

Reviewer : Vivian Levy

1. In the Background, the authors need to present clearer data on HBV population rates in Korea. The first and second sentence should list population (per 100,000 persons) rates of liver cancer and not absolute numbers.

   **Response:**

   As per the reviewer’s comment, the authors revised the text and added the following sentences:

   “In 2009, liver cancer was the second most-frequent cause of cancer death in the Republic of Korea (33.0/100,000 men and 11.4/100,000 women). In the same year, 47.9/100,000 men and 16.2/100,000 women developed liver cancer, accounting for 12.0% of cancer incidence in men and 4.3% in women.” (Page 3, line 51-54)

   “Although its prevalence has decreased from 8.6% in 1980 to 3.2% in 2009, the Republic of Korea is a HBV endemic area.” (Page 3, line 58-59)

2-1. The Background second paragraph states that “horizontal transmission of HBV is an important source of infection in HBV endemic areas” but horizontal transmission is
exceedingly more common in pediatric populations. A stronger case needs to be made that vaccination is an important use of public health resources in older adults.

What is the incidence of acute hepatitis B infections in Korean adults?

Response:

According to Lee et al. [1], the age-specific curves for HBsAg and/or anti-HBs positivity are very similar to those reported before the introduction of the vaccination program. Indeed, HBV infection occurs frequently in adulthood. In Korea, the incidence of acute hepatitis B was 17 per 100,000 in the early 2000s, and was highest in those who were born before the introduction of the HBV vaccination program [2, 3]. Other cohort studies from Korea also suggest that HBV infection occurs frequently in adulthood [1]. Based on these results, one review article suggested that HBV transmission still occurs in unvaccinated and uninfected Korean adults and that HBV vaccination could prevent the spread of infection within a family or via direct contact during adulthood. Therefore, an adult without a complete set of vaccinations should receive catch-up HBV vaccinations [3].

As per the reviewer’s comment, the authors revised the text and added the following sentences:

“Although vertical transmission of HBV is the main source of infection, horizontal transmission is also important in HBV-endemic areas. In Korea, HBV transmission occurs commonly in adulthood, which could be prevented by HBV vaccination. This includes the spread of infection through sexual contact, non-sexual transmission among family members in the same household, direct contact during adulthood, and occupational/health-care related sources. Therefore, catch-up vaccination of adults is critical for the control of HBV infection and subsequent liver cancer.” (Page 3-4, line...
2-2. Sexual transmission would be less likely in an older cohort such as this one where 93% of men are married.

Response:

Most of our study population (93.4%) was married, and the risk of sexual transmission of HBV might be low in this population. However, 26.6% of married people in Korea reported having sex with someone other than their partner, and the rate of concurrent sexual partnerships was more than twice as high as among men than among women [4]. Therefore, we could not exclude possibility of sexual transmission of HBV among adults.

Additionally, although many previous studies have shown that sexual contact carries a much greater risk of HBV infection than do other modes of horizontal transmission, a previous report from Korea suggested that other routes of horizontal HBV infection, such as household (non-sexual) or occupational/healthcare-related contact, may also be important causes of HBV infection [5]. Therefore, the authors propose that horizontal transmission, including both sexual and nonsexual contact, is an important mode of HBV transmission in Korean adults.

As per the reviewer’s comment, the authors revised the text and added the following sentences:

“In Korea, HBV transmission occurs commonly in adulthood, which could be prevented by HBV vaccination. This includes the spread of infection through sexual contact, non-sexual transmission among family members in the same household, direct contact during adulthood, and occupational/health-care related sources” (Page
2-3. What is the prevalence of hepatitis B chronic infection in Korean adults.

**Response:**

Although data regarding the prevalence of chronic hepatitis B infection in Korea were not available, data on HBsAg prevalence were available. We added the following text regarding the prevalence of HBsAg:

“Although its prevalence has decreased from 8.6% in 1980 to 3.2% in 2009, the Republic of Korea is a HBV endemic area.” (Page 3, line 58-59)

2-4. Importantly, this study did not collect biological specimens for hepatitis B surface antigen (to corroborate chronic infection) or hepatitis B surface antibody (to corroborate prior seroprotection).

**Response:**

As per the reviewer’s comment, the Discussion section included an explanation to the effect that we did not collect and analyze biological specimens but relied on self-reported information. As noted below, this is the most important limitation:

“HBV infection status, which was used as an exclusion criterion, was based on self-reports of previous HBV infection instead of the results of serology tests. Therefore, we did not confirm whether participants had been exposed to previous acute or chronic infection with HBV (HBsAg and anti-HBc), introducing the possibility of erroneous data resulting from information bias. Additionally, data on vaccination history and sociodemographic characteristics were based solely on self-reporting.
Measurement of serum total anti-HBs may be a more reliable means of determining the vaccination status of the participants. However, considering 10-15% of those who complete three-dosage series of HBV vaccine fail to response (anti-Hbs level below 10 mIU/ml), it also has some limitations.” (Page 11, line 230-239)

2-5. Given the presumed high prevalence of chronic HBV infection in Korea, biological screening with HBsAg and anti-HBs should have been done on all men prior to vaccination.

**Response:**

In Korea, the government-sponsored nationwide health examination for those who are 40 years of age includes tests for HBsAg and anti-HBs; those without anti-HBs are recommended to get an HBV vaccination. The National Cancer Screening Program in Korea provides liver cancer screening (alpha-fetoprotein and ultrasonography) every 6 months for persons who are at high risk of liver cancer. Beneficiaries of the Medical Aid Program in Korea offered free HBsAg tests.

However, routine HBsAg and anti-HBs prior to vaccination are not recommended for the Korean general population. Additionally, the US Centers for Disease Control and Prevention do not recommend routine pre-vaccination testing because it has not been found to be cost-effective [6]. Moreover, people who have already been infected with HBV will not benefit from or be hurt by vaccination [7]. Therefore, the authors propose that biological screening with HBsAg and anti-HBs is not necessary prior to vaccination for members of the general population.

2-6. Men who were chronically infected should have been linked to hepatoma screening
and HBV treatment services.

Response:

The authors describe the national liver cancer screening program for groups at high risk of liver cancer, such as HBsAg carriers, in the Discussion section:

“To address the secondary prevention of liver cancer, the National Cancer Screening Program in Korea began an initiative for liver cancer screening in 2003. The program provides liver cancer screening (alpha-fetoprotein and ultrasonography) every 6 months for persons aged 40 or older who are positive for HBsAg, anti-HCV, or liver cirrhosis.” (Page 9, line 187-190)

3. In Methods section, more details are needed about recruitment. Was this a national, population based, probability sample or some other type of sample? In the Methods, first paragraph, sentence reference to exclusion of participants, the authors need to specify if all or any men were tested for HBsAg or anti-HBs as part of this study. If not, this needs to be highlighted as a significant limitation of this study.

Response:

As per the reviewer’s comment, the authors revised the text and added the following sentences:

“The Korean National Cancer Screening Survey (KNCSS) is an annual nationwide population-based cross-sectional interview survey using multi-stage random sampling to investigate participation rates in screening for gastric, liver, colorectal, breast, and cervical cancers in representative samples.” (Page 5, line 92-95)

“Among the 2,441 men included initially, we excluded 152 subjects who, by self-
report, had existing health problems related to hepatitis infection, *(i.e.,* liver cirrhosis), were HBsAg-positive, and/or had chronic infection associated with hepatitis C. We further excluded 52 men due to the presence of hepatitis B surface antibodies (anti-HBs) prior to vaccination as well as 63 others due to missing information pertaining to major variables. Data from 2,174 men were used in the final analyses.”*(Page 5, line 101-106)*

“HBV infection status, which was used as an exclusion criterion, was based on self-reports of previous HBV infection instead of the results of serology tests. Therefore, we did not confirm whether participants had been exposed to previous acute or chronic infection with HBV (HBsAg and anti-HBc), introducing the possibility of erroneous data resulting from information bias.”*(Page 11, line 230-234)*

“Measurement of serum total anti-HBs may be a more reliable means of determining the vaccination status of the participants. However, considering 10-15% of those who complete three-dosage series of HBV vaccine fail to response (anti-Hbs level below 10 mIU/ml), it also has some limitations.”*(Page 11, line 236-239)*

4. Also in the Methods section, more information should be provided about where HBV vaccination was done? In local public health clinics, home visits? Specify exactly what type of HBV vaccine was given.

**Response:**

We did not ask about the location at which the HBV vaccination was given or about the type of HBV vaccine received. Both recombinant HBV and plasma-derived vaccines have been used in Korea, although production of plasma-derived vaccine was discontinued in 2004. Although the standard schedule of administration of the two types of vaccines differs (0, 1, 6 months for the recombinant HBV vaccine and 0,
1, 2 months for the plasma-derived vaccine), we asked about the number of HBV vaccinations received and defined complete and incomplete vaccination according to this number. Thus, we do not believe that asking about the type of HBV vaccine would have substantially affected the results.

The authors added lack of awareness about the type of HBV vaccine to the limitations of this study. The following text was added to the Discussion section:

“Furthermore, despite the fact that both recombinant and plasma-derived HBV vaccines were used in Korea until 2004, we did not ask participants about the type of HBV vaccine received. The type of vaccine administered determines which one of two standard schedules is used; the 0, 1, 6 schedule is applied when vaccinating with recombinant HBV, whereas the 0, 1, 2 schedule is applied when using plasma-derived vaccine. Such differences between the two HBV vaccines may have affected the accuracy of the reports of vaccination history.” (Page 12, line 245-251)

We also added the following information regarding how Koreans receive the HBV vaccine:

“In Korea, HBV vaccination is offered by a wide range of healthcare facilities, including local public health clinics, primary healthcare settings, and tertiary hospital facilities and the costs of HBV vaccination for adults are relatively low (3–30 $US). HBV vaccine costs are considerably lower when administered in public health clinics than in private hospitals.” (Page 9, line 176-179)

5. In Methods, section should clarify if polychotomous logistic regression refers to multivariate and if yes, use this term instead.

Response: Thank you for your comment.
However, polychotomous logistic regression differs from multivariate logistic regression. Multivariate logistic regression has more than one independent variable as well as dependent variables with two levels. However, polychotomous logistic regression uses independent variables and dependent variables with three or more levels. This study used three levels of dependent variables (complete vaccination, incomplete vaccination, and non-vaccination). Therefore, we believe that “polychotomous logistic regression” might be better.

6. In Methods, the term “private insurance for cancer” is not clear. Does this mean vaccination, cancer treatment or both are covered? This term needs to be better defined.

Response:

Supplemental insurance is extra or additional insurance that people can purchase to help them pay for services and out-of-pocket expenses which regular insurance does not cover. Because the coverage provided by Korean National Health Insurance, which is mandatory for the entire population, is limited with respect to cancer (about 64%), some people obtain supplemental insurance.

In response to this comment, we changed “private insurance for cancer” to “supplemental medical insurance for cancer”.

7. In Results, fourth paragraph, the main reason given for not being vaccinated is “not knowing the necessity of HBV vaccination.” Was there any education of participants regarding utility of vaccination? If yes, this should be specified in Methods and exactly what education was offered. If not, this should be clearly stated in the Methods
Response: Thank you for your comment.

We asked participants who were never vaccinated whether they knew that they needed to do so to understand their background knowledge. We did not conduct any interventions, such as education, regarding the need for vaccination.

In response to this comment, we revised the Method section as follows:

Non-vaccinated men were asked to choose one of the following reasons for not being vaccinated: “Did not know I need HBV vaccination”, “Put it off due to feeling annoyed about it”, “Forgot”, “Lack of time”, “Did not know the severity of the sequelae of HBV infection”, and “Other”. (Page 6, line 115-118)

8. In Discussion, second to last chapter on limitations, one of the major limitations of this study is that biological markers were not collected prior to vaccination. I would cite studies which show self report of vaccination status is not reliable. An example is:


Topp L, Day C, Dore GJ, Maher L.

Response:

As per the reviewer’s comment, the authors revised the text and added the following sentences in the Discussion section:

“Measurement of serum total anti-HBs may be a more reliable means of determining the vaccination status of the participants. However, considering 10-15% of those who complete three-dosage series of HBV vaccine fail to response (anti-Hbs level below 10 mIU/ml), it also has some limitations. We did not review participants’
medical records and consequently could not verify HBV vaccination status. Previous studies have reported different results regarding the reliability of self-reported vaccination history. Some suggested that self-reported vaccination history and personal information are reliable in that they are consistent with the health information documented in medical records but a study have found opposite results. Information bias may have led to inaccurate information about vaccination status.”

(Page 11-12, line 236-245)

9. In Conclusion section, the first sentence states “horizontal transmission is one of the main routes of transmission in endemic areas”. There is extensive literature that horizontal and vertical transmission is important in pediatric populations in Asia, a more convincing case needs to be made that this is true for predominantly heterosexual Korean men.

**Response:**

According to Lee et al., the age-specific curves for HBsAg and/or anti-HBs positivity were very similar to those before the introduction of the vaccination program. Indeed, HBV infection occurs frequently during adulthood. Other cohort studies from Korea also suggest that HBV infection occurs frequently in adulthood [1]. Based on these results, one review article suggested that HBV transmission in Korea still occurs in unvaccinated and uninfected adults and that HBV vaccination could prevent the spread of infection within a family or via direct contact during adulthood [3]. Therefore, we suggest that horizontal transmission in adulthood is also an important source of HBV infection among Korean adults.

Following the reviewer’s comment, the authors revised the Introduction and
Conclusions as follows:

“Although vertical transmission of HBV is the main source of infection, horizontal transmission is also important in HBV-endemic areas. In Korea, HBV transmission occurs commonly in adulthood, which could be prevented by HBV vaccination. This includes the spread of infection through sexual contact, non-sexual transmission among family members in the same household, direct contact during adulthood, and occupational/health-care related sources” (Page 4, line 75-79)

“Although vertical transmission of HBV is the main source of infection, horizontal transmission is also important in HBV-endemic areas, especially in Korea, where HBV infection commonly occurs during adulthood.” (Page 13, line 278-280)

10. Figure 1 should be renamed, “Vaccination series completion of hepatitis B virus vaccination…”

Response:

Following the reviewer’s comment, the authors revised as below

“Figure 1. Rate of vaccination series completion of hepatitis B virus (HBV) according to age among 2,174 men, Korean National Cancer Screening Survey, 2006–2008.”

11. Table 1, for the variable “area of residence” the difference between Metropolitan and Urban should be specified. “Private insurance for cancer” variable should be defined in Methods.

Response:
Following the reviewer’s comment, the authors added footnote to Table 1 and revised “Private insurance for cancer” to “Supplemental medical insurance for cancer” (Page 18)

“Metropolitan population ≥ 1.2 million; Urban population ≥ 50,000; Rural population < 50,000.” (Page 18)

12. Table 2. “Complete vaccination” and “Incomplete vaccination” should be top terms in columns.

Response:
Following the reviewer’s comment, we revised the top terms in columns of Table 2 as “Complete vaccination” and “Incomplete vaccination”. (Page 19)

Minor essential revisions
1. In Methods, first paragraph, sentence “Among the 2,441 men…” Recommend remove the word “antibody” after “hepatitis C” and simply refer to as “hepatitis C chronically infected.” Sentence that follows should include the word “surface” before antibodies: “We further excluded 52 men….presence of hepatitis B surface antibodies before vaccination,… “

Response:
Following the reviewer’s comment, the authors revised as below

“Among the 2,441 men included initially, we excluded 152 subjects who, by self-report, had existing health problems related to hepatitis infection, (i.e., liver cirrhosis), were HBsAg-positive, and/or had chronic infection associated with hepatitis C. We further excluded 52 men due to the presence of hepatitis B surface
antibodies (anti-HBs) prior to vaccination as well as 63 others due to missing information pertaining to major variables. Data from 2,174 men were used in the final analyses.” (Page 5, line 101-106)

2. In Discussion, first paragraph and throughout, would use terms “higher income” and “higher education” instead of “monthly individual income” or “duration of education”

Response: In response to this comment, we revised as below

“In the current study, factors associated with complete HBV vaccination included higher income, higher level of education, and supplemental medical insurance for cancer.” (Page 9, line 169-171)
Reviewer: Elke Leuridan

Major Compulsory Revisions

1. Interesting data, the English should be checked by a native speaker.

   **Response:** In response to this comment, the English was checked by two native speakers of English, and we included a certificate to document this process.

2. Methodology: it is unclear why women are not included and why the incidence of HBV infection is higher in men. Horizontal transmission is not a plausible explanation.

   In high endemicity countries, vertical transmission is known to be the major source of infection, not horizontal transmission.

   **Response:**

   In the authors’ opinion, the HBV vaccination/infection rates of Korean females and males should be investigated separately because HBV vaccination/infection in women contributes to both horizontal and vertical transmission, whereas that in men contributes only to horizontal transmission. Additionally, Korea has a national program to prevent the vertical transmission of HBV. This program involves screening all pregnant women for HBsAg and giving newborns with HBsAg-positive mothers hepatitis B immunoglobulin and the HBV vaccine at the time of delivery. Therefore, women have more opportunities to understand their HBV infection status and the need for an HBV vaccination.

   In some Asian countries, the prevalence of HBV is higher in men than in women. In both Korea and Thailand, the prevalence of HBsAg was higher in men (8–10% of males and 6–8% of females) [8]. To the authors’ knowledge, no research investigating differences in HBV infection rate by sex is available. However, we
might suggest that programs to prevent vertical transmission, from mother to newborn, may explain the lower prevalence in females living in HBV endemic areas. According to Lee et al. [1], the age-specific curves for HBsAg and/or anti-HBs positivity are very similar to those before the introduction of the vaccination program. Indeed, HBV infection occurs frequently during adulthood. In Korea, the incidence of acute hepatitis B was 17 per 100,000 in the early 2000s, and was highest in those who were born before the introduction of the HBV vaccination program [2, 3]. Other cohort studies from Korea also suggest that HBV infection occurs in adulthood [1]. Based on these results, one review article suggested that HBV transmission in Korea still occurs in unvaccinated and uninfected adults and that HBV vaccination could prevent the spread of infection within a family or via direct contact during adulthood. Therefore, an adult without a complete set of previous vaccinations should receive catch-up HBV vaccinations [3].

As per the reviewer’s comment, the authors revised this section as follows:

“Although vertical transmission of HBV is the main source of infection, horizontal transmission is also important in HBV-endemic areas. In Korea, HBV transmission occurs commonly in adulthood, which could be prevented by HBV vaccination. This includes the spread of infection through sexual contact, non-sexual transmission among family members in the same household, direct contact during adulthood, and occupational/health-care related sources.” (Page 3-4, line 73-79)

3. Methodology: Table 4: how was the question posed? It seems that people could only choose 1 of the options. If you correlate duration of education with knowledge, you should find the same trend between duration of education and the other reasons for not
vaccinating, which is not true! Besides, there is no p-value indicated in table 2 for occupation. Did you look for influences between the different variables, e.g. duration of education and occupation? The same trend should be found for occupation if your hypothesis holds true.

**Response:**

Participants provided only one reason for not being vaccinated. As per the reviewer’s comment, the authors revised this section as follows:

“Non-vaccinated men were asked to choose one of the following reasons for not being vaccinated: “Did not know I need HBV vaccination”, “Put it off due to feeling annoyed about it”, “Forgot”, “Lack of time”, “Did not know the severity of the sequelae of HBV infection”, and “Other.” (Page 6, line 115-118)

We speculated that ignorance about needing an HBV vaccination may have reflected the lack of background information about HBV infection and the risk factors for liver cancer, one of the major types of cancer in Korea. We attempted to investigate the relationship between educational level and background information about HBV infection and risk factors for liver cancer. We believe that other reasons for not being vaccinated were less likely to reflect the background of respondents.

We did not show the value of the $p$-trend for occupation because this measure was applied to determine whether associations between independent variables with more than two categories were linear [9, 10]. The use of $p$-trends requires that independent variables are ordinal. As the authors considered occupation (managerial and professional, service and sales, routine and manual, and long-term unemployed) to be nominal rather than ordinal, we did not present $p$-trend data.

We conducted interaction tests between independent variables but found no
interactions. Therefore, it is possible that the variables had minimal influence on one another, and we added the following sentences to the text:

“Interaction tests were also conducted by including interaction terms between independent variables..” (Page 6, line 123-124)

4. Methodology: Why did you exclude hepatitis B carriers or people who had the disease? They can have been vaccinated too. What risk factors did they have for not being vaccinated?

Response:

Although hepatitis B carriers may be vaccinated, many studies have suggested that the HBV vaccine has limited or no effect on HBsAg carriers [11]. Therefore, we thought that the inclusion of hepatitis B carriers would have limited implications. We also excluded those who were chronically infected with hepatitis C because HBV/HCV co-infection is not uncommon, particularly in high-endemic areas. Indeed, 5–7% of patients infected with HBV were positive for HCV and 2–10% of patients with chronic hepatitis C were positive for HBV [12, 13]. Additionally, of those who met one of the exclusion criteria, liver cirrhosis, 56% were HBsAg-positive, 10% were anti-HCV-positive, and 3% were infected with both HBV and HCV [14]. This condition has a shared etiology with HBV and HCV. Therefore, we excluded men positive for anti-hepatitis C antibodies.

We understood being a HBV carrier to imply not only the lack of vaccination but also the ineffectiveness of HBV vaccination; we tried to exclude those with diseases that shared an etiology with HBV infection.
5. Discussion: if you hypothesize that horizontal transmission is the main reason for the high incidence of HBV infection in Korean men, then targeting risk groups would be more effective (blood transfusion recipients, homosexuals, ivdu…) If this hypothesis is right, then why would women be less infected?

Response:

Following the reviewer’s comment, the authors revised Introduction section as below:

“Although vertical transmission of HBV is the main source of infection, horizontal transmission is also important in HBV-endemic areas. In Korea, HBV transmission occurs commonly in adulthood, which could be prevented by HBV vaccination. This includes the spread of infection through sexual contact, non-sexual transmission among family members in the same household, direct contact during adulthood, and occupational/health-care related sources.” (Page 3-4, line 73-79)

As noted in the Introduction, previous studies of HBV vaccination focus on at-risk groups (page 4, line 85–86). However, we believe that HBV vaccination status needed to be investigated among the general adult population in endemic areas, in which HBV transmission occurs commonly in adulthood and HBV vaccination could prevent the spread of infection through sexual contact, through non-sexual contact within families, through direct contact during adulthood, or through occupational/healthcare-related contact. Therefore, we did not restrict our focus to high-risk groups but instead targeted the general male population.

In some Asian countries, the prevalence of HBV is higher in men than in women. In both Korea and Thailand, the prevalence of HBsAg is higher in men (8–10% of males and 6–8% of females) [8]. To our knowledge, no research investigating the differences in HBV infection rate by sex is available. However, we might suggest
that programs to prevent vertical infection, from mother to newborn, may explain the lower prevalence in females living in endemic areas of HBV.

Minor Essential Revisions

1. Title: please delete the question mark.

   **Response:**

   Following the reviewer’s comment, the authors revised the title as below.

   “Determinants of suboptimal hepatitis B vaccine uptake among men in the Republic of Korea: Where should our efforts be focused: Results from cross-sectional study”  
   (Page 1, line 1-3)

Abstract

2. 1st sentence: is 19.4% the % of liver cancer of HBV? This is not clear.

   **Response:**

   Following the reviewer’s comment, the authors revised the sentence as below.

   “Liver cancer is the second most-frequent cause of cancer death in Korea. Hepatitis B virus (HBV) infection is a major cause of liver cancer, and this disease is effectively prevented by HBV vaccination.” (Page 2, line 26-28)

3. It is unclear from the abstract whether the Korean men are supposed to be vaccinated or not.

   **Response:**

   Following the reviewer’s comment, the authors revised the sentence as below.
“Hepatitis B virus (HBV) infection is a major cause of liver cancer, and this disease is effectively prevented by HBV vaccination. This study was conducted to investigate factors associated with the lack of HBV vaccine uptake in the general adult male population in Korea.” (Page 2, line 27-29)

4. First paragraph: ‘factors associated with the lack of HBV vaccine uptake’ instead of ‘associated with HBV vaccine uptake’.

Response:

Following the reviewer’s comment, the authors revised the sentence as below.

“This study was conducted to investigate factors associated with the lack of Hepatitis B virus (HBV) vaccine uptake in the general adult male population in Korea.” (Page 2, line 28-29)

5. Results paragraph: what do you mean with a p-trend? Is this a p value? Please show for all factors the same statistics, why do you show a p value and an odds ratio?

Response:

P-trends are used to determine whether associations between independent variables with more than two categories and a dependent variable are linear by treating the independent variable as continuous [9, 10]. P-trends are often used in epidemiological studies involving independent variables with three or more categories [9, 10], and differ from p-values.

6. “low complete vaccination rate” do you mean low “rate of full vaccination”?

Response:
Following the reviewer’s comment, the authors revised the sentence as below.

“Compared with men who had completed the vaccination regimen, non-vaccinated men were more likely to lack supplemental medical insurance for cancer (odds ratio = 0.66, 95% confidence interval: 0.52–0.84), have lower incomes ($p$-trend = 0.010), and be less educated ($p$-trend = 0.021).” (Page 2, line 35-38)

Background

7. Please add years from the references 3 and 4. Do you have more recent data? How many of the liver cancer cases in 2008 in Korea were due to chronic HBV infection?

Response:

Of the 6,027 cases of hepatocellular carcinoma (HCC), 4,856 were attributed to HBV infection, accounting for 68.1% of HCC cases and deaths in Korea [15].

Following the reviewer’s comment, the authors revised the sentence as below and updated the reference.

“Worldwide, the rate of liver cancer development due to chronic HBV infection was 0.1%/person-year in 1997. In Korea, the rate was 0.8%/year, and the 5-year cumulative incidence was 3% in 2009.” (Page 3, line 60-62)

“Of the 6,027 cases of hepatocellular carcinoma (HCC), 4,856 were attributed to HBV infection, accounting for 68.1% of HCC cases and deaths in Korea” (Page 3, line 56-58)

8. The sentence referring to reference 5: please add the time interval in this study. Are there any more recent data from Korea?

Response:
We did not find more recent data from Korea. Following the reviewer’s comment, the authors revised the sentence as below.

“Another study conducted in Korea reported that during the 20-year period from 1972 to 1992, 26% of HBV-infected individuals developed primary liver cancer as a result of the HBV infection” (Page 3, line 62-64)

9. Next line: prevents liver cancer effectively, please delete ‘effectively’

Response:

Following the reviewer’s comment, the authors revised the sentence as below.

“The HBV vaccine was the first cancer-preventive vaccine, which prevented liver cancer” (Page 3, line 65-66)

10. Last sentence of page 3: prevalence of HBV in which age cohort?

Response:

Following the reviewer’s comment, the authors revised the sentence as below.

“In 2009, in Korea, the prevalence of hepatitis B surface antigen (HBsAg) and its sequelae was much higher among adult male compared with adult women or teenagers, who had been chosen as the target group in the nationwide HBV vaccination program.” (Page 4, line 81-83)

11. Page 4: this recommendation/interpretation fits better in the discussion, not in the background.

Response:
As per the reviewer’s comment, we moved the following sentence to the Conclusions:

“To increase the rate of complete HBV vaccination it may be necessary to develop tailored approaches that take into account the various factors associated with vaccine uptake.” (Page 13, line 280-282)

12. Catch up programme: which age cohort was targeted? Children programme: please add the age and schedule you use in children.

Response:

Catch-up vaccination programs are directed at adults who did not receive an HBV vaccine. The nationwide HBV vaccination program was conducted for infants using the 0, 1, 6 month schedule. According to the reviewer’s comment, the authors revised the sentence as follows:

“In 1995, the nationwide HBV vaccination program for infants with 0, 1, 6 months schedule was implemented by the National Immunization Program as part of the Communicable Diseases Prevention Act.” (Page 3, line 70-72)

13. What is the prevalence in your country of HBV? What is the rate of vertical transmission in your country?

Response:

According to the reviewer’s comment, the authors revised the sentence as follows:

“Although its prevalence has decreased from 8.6% in 1980 to 3.2% in 2009, the Republic of Korea is a HBV endemic area.” (Page 3, line 58-59)
Studies regarding vertical transmission of HBV were mostly conducted in Korea in 1980s. Korea has a national program to prevent the vertical transmission of HBV. This program involves screening all pregnant women for HBsAg and giving newborns with HBsAg-positive mothers hepatitis B immunoglobulin and the HBV vaccine at 0, 1 and 6 months of age. Failure rate of giving hepatitis B immunoglobulin and HBV vaccination to children with HBsAg-positive mothers is only 4.2% [3], and the rate of vertical infection of HBV is suggested to be low.

Methods

14. How do you explain the difference with women in Korea? It would be nice to compare with vaccination data in women.

**Response:**

Following the reviewer’s comment, the authors added in the Discussion section as follows:

“It is noteworthy that 39.8% of Korean women received the complete vaccination, a higher rate than among Korean men. One reason for this difference might be the fact that the program for the prevention of vertical HBV transmission targeted all pregnant women in Korea.” (Page 9, line 183-186)

14. KNCSS: why are men included from 40 years on and women from 30 years on?

**Response:**

The main objective of the Korean National Cancer Screening Survey (KNCSS) is to investigate rates of participation in screening programs for gastric, liver, colorectal, breast, and cervical cancers among representative samples. Because the target
population of the Korean “National Cancer Screening Program” was defined according to the following criteria, cancer-free men aged 40 years or over and cancer-free women aged 30 years were included. As per the reviewer’s comment, we revised the text as follows:

**Protocols of the National Cancer Screening Program**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Target Population</th>
<th>Interval</th>
<th>Test or Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>Age 40 &amp; Over</td>
<td>2 years</td>
<td>Endoscopy or UGI</td>
</tr>
<tr>
<td>Liver</td>
<td>Age 40 &amp; Over</td>
<td>1 year</td>
<td>Sonography &amp; AFP</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Age 50 &amp; Over</td>
<td>1 year</td>
<td>FOBT: in case of an abnormal result, Colonoscopy or DCBE</td>
</tr>
<tr>
<td>Breast</td>
<td>Age 40 &amp; Over Woman</td>
<td>2 years</td>
<td>Mammography</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>Age 30 &amp; Over Woman</td>
<td>2 years</td>
<td>Pap smear</td>
</tr>
</tbody>
</table>

“Based on target populations identified in an organized cancer screening program conducted by the Republic of Korea, cancer-free men 40 years and older and cancer-free women 30 years and older comprise the KNCSS-eligible population.” (Page 5, line 95-97)

**Results**

15. What do you mean with p-trend? Is this a p-value?

**Response:**

*P*-trends are used to determine whether associations between independent variables with more than two categories and a dependent variable are linear by treating the independent variable as continuous [9, 10]. *P*-trends are often used in
epidemiological studies involving independent variables with three or more categories [9, 10], and differ from \( p \)-values.

16. Income categories: please describe in your methods section how you decided on the cutoff of your income categories.

**Response:**

According to the reviewer’s comment, the authors revised the sentence as follows:

“Monthly individual income was classified into four categories: \( \leq $999, $1,000–$1,999, $2,000–$3,499, \) and \( \geq $3,500 \) (US currency).” (Page 5-6, line 114-115)

17. Third paragraph page 7: shorter duration of education was associated with both complete and incomplete vaccination: this is in contradiction to the previous sentence: I guess it should be: education was associated with!

**Response:**

According to the reviewer’s comment, the authors revised the sentence as follows:

“The higher level of education was correlated with both the complete and incomplete HBV vaccination when compared with the non-vaccinated group (\( p \)-trend = 0.021 and < 0.001, respectively).” (Page 7, line 143-145)

18. Next sentence on lower monthly income: ‘lower complete’, do you mean incomplete? But further you say, not associated with incomplete. What do you mean with “lower complete”?

**Response:**

According to the reviewer’s comment, the authors revised the sentence as follows:
“Lower monthly individual income was also associated with a lower rate of complete vaccination ($p$-trend = 0.010) compared to that in unvaccinated men.”

(Page 7, line 145-146)


**Response:**

The authors revised the sentence as follows:

“Additionally, men between 60 and 69 years of age were more likely to receive the full three-dose regimen than were those 40–49 years of age and those who felt their health status was poor completely vaccinated more (Table 3).” (Page 7, line 152-154)

20. Probably it is a language issue but it is weird to repeat every time ‘compared to unvaccinated men’. Besides, it is always compared to vaccinated men.

**Response:**

In polychotomous logistic regression used in our analysis, the odds ratios for complete vaccination (complete 3 series of HBV vaccination) and incomplete vaccination (although they received HBV vaccine but did not complete 3 series (1 or 2 doses)) was presented as the value compared with unvaccinated people (Those who had never received HBV vaccine). Through English check, we tried not to repeat ‘compared to unvaccinated men’ as possible.

21. P8: what do you mean with “put it off ” table 4

**Response:**

Reflecting the reviewer’s comment, the authors revised the ‘put it off’ as ‘Put it off
due to feeling annoyed about it” (Page 6, line 117 and Page 22)

Discussion

22. First paragraph: please re write, this sentence is unclear

Response:

According to the reviewer’s comment, the authors re-wrote the sentence as follows:

“This is the first study to investigate the factors associated with HBV vaccine uptake, an effective medical intervention for the prevention of liver cancer in the general adult male population in Korea. In the current study, factors associated with complete HBV vaccination included higher income, higher level of education, and supplemental medical insurance for cancer. Level of education was significantly associated with incomplete versus non-vaccinated status with complete versus incomplete vaccination status.” (Page 9, line 167-172)

23. Second paragraph page 9: if you cite an article, make sure to not change the message.

Reference 12 says: seroprotective rates are CLOSELY TO 100% (100% is not possible) and APPROXIMATELY 95%.

Response:

According to the reviewer’s comment, the authors revised the sentence as follows:

“Indeed, after receiving the complete three-dosage series of HBV vaccination, seroprotection rates approached 100% among healthy children and 95% among healthy adults.” (Page 9, line 174-176)
24. P 11: is the cost effectiveness of the national cancer screening program in Korea proven?

**Response:**

The National Cancer Screening Program includes five types of cancer (gastric, liver, colorectal, breast, and uterine cervix cancer). Screening for liver cancer began in 2003, and a cost-effectiveness analysis of these programs is underway. We expect the results to be released in the near future.

25. P10-11: the role of educational level in deciding on HBV vaccination can be discussed in a shorter way, authors do repeat the results and existing evidence several times.

**Response:**

According to the reviewer’s comment, the authors revised as follows:

“Our study revealed that the most common reason for not being vaccinated was lack of fundamental knowledge regarding the necessity of HBV vaccination, which was cited by 40% of non-vaccinated participants. Similarly, a previous study found that lack of awareness about vaccination recommendations was the main barrier to becoming vaccinated. Moreover, as the level of education decreased, the proportion of men answering “Did not know I need HBV vaccination” increased. This finding may reflect disparities in how healthcare information is communicated. People with lower education levels tend to be less aware of their hepatitis-infection status when compared with more educated people. This in turn could affect liver cancer screening, because only high-risk groups, such as hepatitis carriers or liver cirrhosis patients, are targeted by the National Cancer Screening Program in Korea. As a result, it is not
surprising that the burden of liver disease is much greater among less educated people. In Korea, inequality in liver cancer mortality exists; higher mortality rates due to liver cancer have been associated with lower levels of education. Our results indicate the importance of focus efforts on health education of less educated groups and underscore the necessity of increasing HBV vaccination uptake.” (Page 10-11, line 215-229)

26. The study would be much more interesting if also women would be included. Horizontal transmission as the reason for higher incidence of HBV in men, is not plausible, since horizontal transmission is known to happen between young children. Sexual transmission implies women.

Response:

In the authors’ opinion, the HBV vaccination/infection rates of Korean women and men should be investigated separately because HBV vaccination/infection in women contributes to both horizontal and vertical transmission, whereas that in men contributes only to horizontal transmission. Additionally, Korea has a national program to prevent the vertical transmission of HBV. This program involves screening all pregnant women for HBsAg and giving newborns with HBsAg-positive mothers hepatitis B immunoglobulin and the HBV vaccine at delivery. Therefore, women have more opportunities to understand their HBV infection status and the need for HBV vaccination. Men lack exposure to such information.

In Korea, HBV transmission frequently occurs in adulthood, and HBV vaccination could prevent the spread of infection through sexual contact, non-sexual transmission among family members in the same household, direct contact during
adulthood, and occupational/health-care related sources [1, 3, 5].

References for the reviews comments


8. Merican I, Guan R, Amarapuka D, Alexander MJ, Chutaputti A, Chien RN,


Point-to-Point Responses to the Editorial Requirements

1. Please place tables in main manuscript file rather than additional file.

Response:

Reflecting the editorial requirements, the authors place tables in main manuscript file, after References section. (Page 19-22)

2. Request for consent: Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.

Response:

Reflecting the reviewer’s comment, the authors added the sentence as below.

“Informed consent was obtained from all participants.” (Page 5, line 99)