May 20th, 2022

Dear Dr. Andrzej S Tarnawski,
Editor in chief
World Journal of Gastroenterology

We are sending via web-based submission the revised version of the manuscript Nº 75014: "Insights into the induction of immune response by Hepatitis B vaccine" by Di Lello et al. We would like to thank the reviewers and editors for their comments and suggestions, which were helpful to improve our review. We hope that the revised manuscript will be suitable for publication.
Thank you in advance for your consideration.
Yours sincerely,

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Referee(s)' Comments to Author:

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This is an interesting mini review, but I have a few comments:

1) the clinical effectiveness of vaccination (how different the frequency of hepatitis B infection in the vaccinated and unvaccinated groups) should be described, if the data are available;

***Author´s reply*:** Manuscript was changed following the reviewer´s suggestion. The following paragraph was introduced in the revised version of the manuscript (page 9):

“Although, as previously mentioned, the massive implementation of the HBV vaccine substantially reduced the incidence and prevalence of the infection, few works have addressed the effectiveness of the vaccine and most of them have been carried out in high endemic countries. In general, a 70 to 94% effectiveness range has been reported, depending mainly on the follow-up time, the exposure risk rate (HBsAg prevalence of the population), and the studied cohort age [错误!未找到引用源。,错误!未找到引用源。, 55]. A recent study has shown an approximately 58% effectiveness in a birth cohort (mean age, 12 years) and 85% in participants ≥20 years old [56]. The lower efficacy observed in the birth cohort could be a consequence of a lower level of exposure.”

18-Garcia D, Porras A, Rico Mendoza A, Alvis N, Navas MC, De La Hoz F, De Neira M, Osorio E, Valderrama JF. Hepatitis B infection control in Colombian Amazon after 15 years of hepatitis B vaccination. Effectiveness of birth dose and current prevalence. Vaccine 2018; **36**: 2721–2726. [PMID 29609968 DOI: 10.1016/j.vaccine.2017.11.004]

23-Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev. 2006; 28:126-35. doi: 10.1093/epirev/mxj010. Epub 2006 Jun 16. PMID: 16782778.

55-Peto TJ, Mendy ME, Lowe Y, Webb EL, Whittle HC, Hall AJ. Efficacy and effectiveness of infant vaccination against chronic hepatitis B in the Gambia Hepatitis Intervention Study (1986–90) and in the nationwide immunisation program. BMC Infect Dis. 2014; 14:7. doi: 10.1186/1471-2334-14-7. PMID: 24397793

56-He WQ, Guo GN, Li C. The impact of hepatitis B vaccination in the United States, 1999-2018. Hepatology. 2021 Dec 2. doi: 10.1002/hep.32265. Epub ahead of print. PMID: 34855999.

2) the mechanism of development of the immunity against HBV after vaccination should be described;

***Author´s reply*:** Manuscript was rearranged following the reviewer´s suggestion and the mechanism of development of the immunity against HBV after vaccination was described. The following paragraph was introduced in the revised version of the manuscript (page 7):

Several studies have shown that HBV vaccines induced both humoral and cellular immunity providing long-term protection [34 错误!未找到引用源。,错误!未找到引用源。]. On the one hand, neutralizing antibodies are elicited and two types of them have been identified. The first type targets the 'a' determinant and neutralizes cell viral penetration by blocking the interaction with heparan sulfate [错误!未找到引用源。], required by the virus at an early stage of hepatocyte entrance [错误!未找到引用源。]. The second type targets the high-affinity receptor-binding site of the HBV Pre-S1 domain and blocks the binding to the NTCP receptor preventing the infection of hepatocytes [错误!未找到引用源。,错误!未找到引用源。]. On the other hand, immune memory cells are generated, which upon contact with the HBV can be activated to expand rapidly. This response has been well demonstrated in studies that administered a booster dose to previously vaccinated persons whose antibody titers had fallen below protective titers [错误!未找到引用源。, 错误!未找到引用源。-0].

34-Said ZN, Abdelwahab KS. Induced immunity against hepatitis B virus. World J Hepatol. 2015; 7(12):1660-70. doi: 10.4254/wjh.v7.i12.1660. PMID: 26140085.

35-Van Damme P, Dionne M, Leroux-Roels G, Van Der Meeren O, Di Paolo E, Salaun B, Surya Kiran P, Folschweiller N. Persistence of HBsAg-specific antibodies and immune memory two to three decades after hepatitis B vaccination in adults. J Viral Hepat. 2019; 26 (9): 1066-1075. doi: 10.1111/jvh.13125. PMID: 31087382.

36-Sureau C, Salisse J. A conformational heparan sulfate binding site essential to infectivity overlaps with the conserved hepatitis B virus a-determinant. Hepatology 2013; 57 (3), 985–994. DOI: 10.1002/hep.26125. PMID: 23161433

37-Schulze A, Gripon P, Urban S. Hepatitis B virus infection initiates with a large surface protein-dependent binding to heparan sulfate proteoglycans. Hepatology. 2007; 46 (6):1759-68. doi: 10.1002/hep.21896. PMID: 18046710

38-Urban S, Bartenschlager R, Kubitz R, Zoulim F. Strategies to inhibit entry of HBV and HDV into hepatocytes. Gastroenterology 2014; 147(1), 48–64. 82. doi: 10.1053/j.gastro.2014.04.030. PMID: 24768844.

39- Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, Huang Y, Qi Y, Peng B, Wang H, Fu L, Song M, Chen P, Gao W, Ren B, Sun Y, Cai T, Feng X, Sui J, Li W. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife 2012; 1: e00049. doi: 10.7554/eLife.00049. PMID: 23150796.

40-Lu CY, Ni YH, Chiang BL, Chen PJ, Chang MH, Chang LY, Su IJ, Kuo HS, Huang LM, Chen DS, Lee CY. Humoral and cellular immune responses to a hepatitis B vaccine booster 15-18 years after neonatal immunization. J Infect Dis. 2008; 197 (10):1419-26. doi: 10.1086/587695. PMID: 18444799.

41-Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, Toomey M, Townshend-Bulson L, Rudolph K, Bulkow L, Spradling PR, Baum R, Hennessy T, McMahon BJ. Antibody Levels and Protection After Hepatitis B Vaccine: Results of a 30-Year Follow-up Study and Response to a Booster Dose. J Infect Dis 2016; **214**: 16-22. [PMID: 26802139. DOI: 10.1093/infdis/jiv748].

42-Wang ZZ, Gao YH, Lu W, Jin CD, Zeng Y, Yan L, Ding F, Li T, Liu XE, Zhuang H. Long-term persistence in protection and response to a hepatitis B vaccine booster among adolescents immunized in infancy in the western region of China. Hum Vaccin Immunother 2017; **13**: 909-915. [PMID: 27874311. DOI: 10.1080/21645515.2016.1250990].

3) The first sentence of the paragraph describing vaccination in Taiwan is not clear.

***Author´s reply*:** This point has been clarified in the text. The paragraph now appears at follows (page 6):

“Taiwan was the first country to implement a massive vaccination program against HBV in 1984 and it is the paradigm of its impact on the control of hepatitis. After 30 years of sustained immunization programs, the prevalence of HBsAg has decreased from 9.8% in the pre-vaccination period to 0.5% in the cohort reached by HBV vaccination protocols [错误!未找到引用源。]. The main reason for Taiwan's success was its high 3-doses hepatitis infant vaccine coverage rate, which increased from 88.9 percent in 1985 [错误!未找到引用源。,错误!未找到引用源。] to 98.1 percent in 2018 [错误!未找到引用源。].

21-Lu FT, Ni YH. Elimination of Mother-to-Infant Transmission of Hepatitis B Virus: 35 Years of Experience. Pediatr Gastroenterol Hepatol Nutr. 2020; **23**: 311-318. doi: 10.5223/pghn.2020.23.4.311. PMID: 32704492.

22-Gust ID. Immunisation against hepatitis B in Taiwan. Gut. 1996;**38** Suppl 2(Suppl 2): S67-8. doi: 10.1136/gut.38.suppl_2.s67. PMID: 8786059.

23- Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev. 2006; **28**:126-35. doi: 10.1093/epirev/mxj010. PMID: 16782778.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is a mini review article on hepatitis B vaccine efficacy in inducing protective immunity against hepatitis B. Briefly, this manuscript is well written.

There was some points I would suggest to add information regarding Page 5 and Figure 2. Taiwan is the paradigm of the HBV vaccination impact on the control of hepatitis. It was the first country to implement the HBV vaccine schedules in 1984 and, after 30 years of sustained vaccination, the prevalence of HBsAg has decreased from 9.8% in the pre-vaccinated period to 0.5% in the cohort reached by HBV immunization protocols [14].

I would suggest to add: The main reason for Taiwan's success was their high 3-doses hepatitis infant vaccine coverage rate, which increased from 88.9 percent in 1985 [A, B] to 98.1 percent in 2018 [C]. As there is no data in Figure 2 in delineating 3-doses infant HB vaccine coverage rate in Taiwan. That's not exact. Please add the below references:

A. Gust ID. Immunisation against hepatitis B in Taiwan. Gut. 1996;38 Suppl 2(Suppl 2): S67-8. doi: 10.1136/gut.38.suppl_2.s67. PMID: 8786059.

B. Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev. 2006; 28:126-35. doi: 10.1093/epirev/mxj010. PMID: 16782778.

C.Lu FT, Ni YH. Elimination of Mother-to-Infant Transmission of Hepatitis B Virus: 35 Years of Experience. Pediatr Gastroenterol Hepatol Nutr. 2020; 23(4):311-318. doi: 10.5223/pghn.2020.23.4.311. PMID: 32704492.

***Author´s reply*:** Following the reviewer's suggestions, this information has been added to the text (page 6) and Figure 2.

Taiwan was the first country to implement a massive vaccination program against HBV in 1984 and it is the paradigm of its impact on the control of hepatitis. After 30 years of sustained immunization programs, the prevalence of HBsAg has decreased from 9.8% in the pre-vaccination period to 0.5% in the cohort reached by HBV vaccination protocols [错误!未找到引用源。]. The main reason for Taiwan's success was its high 3-doses hepatitis infant vaccine coverage rate, which increased from 88.9 percent in 1985 [错误!未找到引用源。,错误!未找到引用源。] to 98.1 percent in 2018 [错误!未找到引用源。].

21-Lu FT, Ni YH. Elimination of Mother-to-Infant Transmission of Hepatitis B Virus: 35 Years of Experience. Pediatr Gastroenterol Hepatol Nutr. 2020; **23**: 311-318. doi: 10.5223/pghn.2020.23.4.311. PMID: 32704492.

22-Gust ID. Immunisation against hepatitis B in Taiwan. Gut. 1996;**38** Suppl 2(Suppl 2): S67-8. doi: 10.1136/gut.38.suppl_2.s67. PMID: 8786059.
23- Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev. 2006; **28**:126-35. doi: 10.1093/epirev/mxj010. PMID: 16782778.

Regarding the different generation types of hepatitis B vaccines, the authors may also do a more detailed review on the differences over the HBsAg+, anti-HBs+, as well as anti-HBc+ seroepidemiology descriptions on this mini review. For example:
Higher disappearance rate of anti-HBs was noted in recombinant group than in plasma group when the subjects reached their youth and young adulthood in Taiwan.
Reference: Hsu SH, Chih AH, Lee YC, Huang KC, Jan CF. Higher disappearance rate of anti-HBs in Taiwanese freshers neonatally vaccinated with recombinant yeast hepatitis B vaccine. Liver Int. 2017 Dec;37(12):1780-1787. doi: 10.1111/liv.13437. Epub 2017 Apr 27. PMID: 28374906.

***Author´s reply*:** Following the reviewer's suggestions, this point has been clarified in the text. The following paragraph has been introduced in the revised version of the manuscript (page 4):

“It is worthy to note that several studies have compared the immune response to the plasma-derived first-generation vaccines to that to the recombinant second-generation ones. Most of the studies showed that the lowering rate of anti-HBs was higher in people receiving the recombinant HBV vaccine. However, plasma-derived vaccines were replaced by the recombinant ones due to safety concerns about human blood-derived products [错误!未找到引用源。-错误!未找到引用源。]. In addition, it has been shown that third-generation vaccines containing the pre-S2 and pre-S1 antigens would induce a higher anti-HBs response than second-generation ones, particularly in people ≥45 years old [错误!未找到引用源。-错误!未找到引用源。]. Moreover, in comparison to plasma-derived vaccines, it has been observed that the HBsAg seropositive rate dropped by about 71% and that the anti-HBc seropositive rate decreased by approximately 65% when recombinant HBV vaccines are used, supporting their higher effectiveness [错误!未找到引用源。].”

2-Kao JT, Wang JH, Hung CH, Yen YH, Hung SF, Hu TH, Lee CM, Lu SN. Long-term efficacy of plasma-derived and recombinant hepatitis B vaccines in a rural township of Central Taiwan. Vaccine. 2009; **27**:1858-62. doi: 10.1016/j.vaccine.2009.01.027. PMID: 19186203.

3-Kim YJ, Li P, Hong JM, Ryu KH, Nam E, Chang MS. A Single Center Analysis of the Positivity of Hepatitis B Antibody after Neonatal Vaccination Program in Korea. J Korean Med Sci. 2017; **32**: 810-816. doi: 10.3346/jkms.2017.32.5.810. PMID: 28378555.

4-Hsu SH, Chih AH, Lee YC, Huang KC, Jan CF. Higher disappearance rate of anti-HBs in Taiwanese freshers neonatally vaccinated with recombinant yeast hepatitis B vaccine. Liver Int. 2017; **37**:1780-1787. doi: 10.1111/liv.13437. PMID: 28374906.

5-Hu YC, Yeh CC, Chen RY, Su CT, Wang WC, Bai CH, Chan CF, Su FH. Seroprevalence of hepatitis B virus in Taiwan 30 years after the commencement of the national vaccination program. PeerJ. 2018; 6:e4297. doi: 10.7717/peerj.4297. PMID: 29472994.

6-Shouval D, Roggendorf H, Roggendorf M. Enhanced immune response to hepatitis B vaccination through immunization with a Pre-S1/Pre-S2/S vaccine. Med Microbiol Immunol. 2015; **204**: 57-68. doi: 10.1007/s00430-014-0374-x. PMID: 25557605.

7-Krawczyk A, Ludwig C, Jochum C, Fiedler M, Heinemann FM, Shouval D, Roggendorf M, Roggendorf H, Lindemann M. Induction of a robust T- and B-cell immune response in non- and low-responders to conventional vaccination against hepatitis B by using a third generation PreS/S vaccine. Vaccine. 2014; **32**: 5077-82. doi: 10.1016/j.vaccine.2014.06.076. PMID: 24975813.

8-Vesikari T, Langley JM, Segal N. Immunogenicity and safety of a triantigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. Lancet Infect Dis 2021; **21**: 1271-1281. PMID: 33989539 DOI: 10.1016/S1473-3099(20)30780-5.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: overall the manuscript is well written. please correct grammar of manuscript by using grammar correction software like grammarly.

***Author´s reply*:** Following the reviewer's consideration, a thorough revision of the manuscript was carried out. Grammar was revised using Grammarly and some sentences were rephrased to improve the text´s readability. In addition, the manuscript was sent for grammar revision to Silvina Heisecke who works in the CEMIC-CONICET Scientific Text Writing and Editing Service belonging to CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas, National Council of Scientific and Technical Research).

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

This is an interesting and well written mini-review on Hepatitis B vaccine efficacy. The review is comprehensive, figures are informative. However, as the reviewers suggested, the following key points are missing,

the mechanism of development of the immunity against HBV after vaccination, regarding the different generation types of hepatitis B vaccines,

***Author´s reply*:** Manuscript has been changed following the Science editor´s suggestion and the mechanism of development of the immunity against HBV after vaccination, regarding the different generation types of hepatitis B vaccines was detailed. The following paragraph has been introduced in the revised version of the manuscript (page 4):

"It is worthy to note that several studies have compared the immune response to the plasma-derived first-generation vaccines to that to the recombinant second-generation ones. Most of the studies showed that the lowering rate of anti-HBs was higher in people receiving the recombinant HBV vaccine. However, plasma-derived vaccines were replaced by the recombinant ones due to safety concerns about human blood-derived products [错误!未找到引用源。-错误!未找到引用源。]. In addition, it has been shown that third-generation vaccines containing the pre-S2 and pre-S1 antigens would induce a higher anti-HBs response than second-generation ones, particularly in people ≥45 years old [错误!未找到引用源。-错误!未找到引用源。]. Moreover, in comparison to plasma-derived vaccines, it has been observed that the HBsAg seropositive rate dropped by about 71% and that the anti-HBc seropositive rate decreased by approximately 65% when recombinant HBV vaccines are used, supporting their higher effectiveness [错误!未找到引用源。]."

2-Kao JT, Wang JH, Hung CH, Yen YH, Hung SF, Hu TH, Lee CM, Lu SN. Long-term efficacy of plasma-derived and recombinant hepatitis B vaccines in a rural township of Central Taiwan. Vaccine. 2009; **27**:1858-62. doi: 10.1016/j.vaccine.2009.01.027. PMID: 19186203.

3-Kim YJ, Li P, Hong JM, Ryu KH, Nam E, Chang MS. A Single Center Analysis of the Positivity of Hepatitis B Antibody after Neonatal Vaccination Program in Korea. J Korean Med Sci. 2017; **32**: 810-816. doi: 10.3346/jkms.2017.32.5.810. PMID: 28378555.

4-Hsu SH, Chih AH, Lee YC, Huang KC, Jan CF. Higher disappearance rate of anti-HBs in Taiwanese freshers neonatally vaccinated with recombinant yeast hepatitis B vaccine. Liver Int. 2017; **37**:1780-1787. doi: 10.1111/liv.13437. PMID: 28374906.

5-Hu YC, Yeh CC, Chen RY, Su CT, Wang WC, Bai CH, Chan CF, Su FH. Seroprevalence of hepatitis B virus in Taiwan 30 years after the commencement of the national vaccination program. PeerJ. 2018; 6:e4297. doi: 10.7717/peerj.4297. PMID: 29472994.

6-Shouval D, Roggendorf H, Roggendorf M. Enhanced immune response to hepatitis B vaccination through immunization with a Pre-S1/Pre-S2/S vaccine. Med Microbiol Immunol. 2015; **204**: 57-68. doi: 10.1007/s00430-014-0374-x. PMID: 25557605.

7-Krawczyk A, Ludwig C, Jochum C, Fiedler M, Heinemann FM, Shouval D, Roggendorf M, Roggendorf H, Lindemann M. Induction of a robust T- and B-cell immune response in non- and low-responders to conventional vaccination against hepatitis B by using a third generation PreS/S vaccine. Vaccine. 2014; **32**: 5077-82. doi: 10.1016/j.vaccine.2014.06.076. PMID: 24975813.

8-Vesikari T, Langley JM, Segal N. Immunogenicity and safety of a triantigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. Lancet Infect Dis 2021; **21**: 1271-1281. PMID: 33989539 DOI: 10.1016/S1473-3099(20)30780-5.

The authors may also do a more detailed review on the differences over the HBsAg+, anti-HBs+.

***Author´s reply*:** The text has been modified following the Science editor´s suggestion and a more detailed review on the differences over the HBsAg+, anti-HBs+ was added to the revised manuscript. The following paragraph was introduced in the revised version of the manuscript (page 9):

“Although, as previously mentioned, the massive implementation of the HBV vaccine substantially reduced the incidence and prevalence of the infection, few works have addressed the effectiveness of the vaccine and most of them have been carried out in high endemic countries. In general, a 70 to 94% effectiveness range has been reported, depending mainly on the follow-up time, the exposure risk rate (HBsAg prevalence of the population), and the studied cohort age [错误!未找到引用源。,错误!未找到引用源。, 错误!未找到引用源。]. A recent study has shown an approximately 58% effectiveness in a birth cohort (mean age, 12 years) and 85% in participants ≥20 years old [错误!未找到引用源。]. The lower efficacy observed in the birth cohort could be a consequence of a lower level of exposure.”

18-Garcia D, Porras A, Rico Mendoza A, Alvis N, Navas MC, De La Hoz F, De Neira M, Osorio E, Valderrama JF. Hepatitis B infection control in Colombian Amazon after 15 years of hepatitis B vaccination. Effectiveness of birth dose and current prevalence. Vaccine 2018; **36**: 2721–2726. [PMID 29609968 DOI: 10.1016/j.vaccine.2017.11.004]

23-Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev. 2006; 28:126-35. doi: 10.1093/epirev/mxj010. Epub 2006 Jun 16. PMID: 16782778.

53-Peto TJ, Mendy ME, Lowe Y, Webb EL, Whittle HC, Hall AJ. Efficacy and effectiveness of infant vaccination against chronic hepatitis B in the Gambia Hepatitis Intervention Study (1986–90) and in the nationwide immunisation program. BMC Infect Dis. 2014; 14:7. doi: 10.1186/1471-2334-14-7. PMID: 24397793

54-He WQ, Guo GN, Li C. The impact of hepatitis B vaccination in the United States, 1999-2018. Hepatology. 2021 Dec 2. doi: 10.1002/hep.32265. Epub ahead of print. PMID: 34855999.

Finally, Authors are strongly recommended to consult with a professional English language editing company to further polish the paper.

***Author´s reply*:** Following the reviewer's consideration, a thorough revision of the manuscript has been carried out. The grammar was revised, and some sentences were rephrased to improve the text´s readability. In addition, the manuscript was sent for grammar revision to Silvina Heisecke who works in the CEMIC-CONICET Scientific Text Writing and Editing Service belonging to

CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas, National Council of Scientific and Technical Research)

Language Quality: Grade C (A great deal of language polishing)
Scientific Quality: Grade B (Very good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: https://www.referencecitationanalysis.com/.

***Author´s reply*:** Reference Citation Analysis was used when revising the manuscript.

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

***Author´s reply*:** Following the suggestion, the figure was provided using PowerPoint to ensure that the editor can reprocess all graphs, arrows or text portions.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

***Author´s reply*:** No tables are included in the current manuscript

Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright

information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Author´s reply: Figure 1 and 3 were originally created by the authors for this manuscript and were not re-used or published elsewhere.

Figure 2 is adapted from Data compiled by the Asian Liver Center at Stanford University 2020. Source: WHO Vaccine-preventable Diseases: monitoring System. 2020 global summary WHO-UNICEF estimates. https://apps.who.int/immunization_monitoring/globalsummary

7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

Step 1: Author Information

Please click and download the Format for authorship, institution, and corresponding author guidelines, and further check if the authors names and institutions meet the requirements of the journal.

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Please check if the manuscript information is correct.

Step 3: Abstract, Main Text, and Acknowledgements

(1) Guidelines for revising the content: Please download the guidelines for Original articles, Review articles, or Case Report articles for your specific manuscript type (Review) at: https://www.wjgnet.com/bpg/GerInfo/291. Please further revise the content your manuscript according to the Guidelines and Requirements for Manuscript Revision.

(2) Format for Manuscript Revision: Please update the format of your manuscript according to the Guidelines and Requirements for Manuscript Revision and the Format for Manuscript Revision.

Please visit https://www.wjgnet.com/bpg/GerInfo/291 for the article type-specific guidelines and formatting examples.

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Step 4: References

Please revise the references according to the Format for References Guidelines, and be sure to edit the reference using the reference auto-analyser.

Reminder: It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

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Lian-Sheng Ma, Editorial Office Director, Company Editor-in-Chief, Editorial Office