December 28, 2020
Resubmission of manuscript **"*H. pylori:* commensal, symbiont or pathogen?"**
Authors: Vasiliy I Reshetnyak, Alexandr I Burmistrov, Igor V Maev
Name of Journal: ***World Journal of Gastroenterology***
ESPS Manuscript No: 61406

Answer for Editor

Dear Lian-Sheng Ma, Science Editor,

We send you revised the manuscript 61406 **"*H. pylori:* commensal, symbiont or pathogen?"** (Please refer to the attached file "revised manuscript 61406") and **Audio core tip** (Please refer to the attached file "61406-Audio Core Tip").

The authors express their gratitude to the reviewers (ID – 04913316; ID – 03818597; ID – 02446277; ID – 02462321) for their work done and comments.

Response to the reviewer ID – 04913316.

The authors express their gratitude to the reviewer for the work done and for the positive evaluation of the manuscript. The links indicated by the reviewer are inserted both in the text of the review and in references (highlighted in green).

Response to the reviewer ID – 03818597.

The authors express their gratitude for the detailed analysis of the manuscript and the comments made. Response to the reviewer according to the comments:

1) When writing the review, the authors briefly touched on the general information about *H. pylori* (HP), considering that with them the manuscript will have a more complete view. The authors hope that the reviewer will not insist on removing these chapters from the review.

2) The authors are familiar with works concerning the impact of eradication of *H. pylori* on reducing the risk of recurrence of ulcers and secondary gastric cancer, which the reviewer suggests to consider in the review (https://doi.org/10.1016/S0140-6736(02)07273-2, https://pubmed.ncbi.nlm.nih.gov/9732917/, https://www.ncbi.nlm.nih.gov/books/NBK68778/). But these references were not included in the manuscript, as the authors tried to adhere to the requirements of the publisher's editorial board and provide information (if any) for the last 10-15 years. The works indicated by the reviewer relate to 1998, 2001 and 2002. Taking into account the reviewer's wishes, the authors inserted the above references in the relevant sections of the manuscript (highlighted in yellow in the text and in the list of references). At the same time, the authors considered it necessary to present some works that indicate a multifactorial etiology of

peptic ulcer (PUD) and gastric cancer (GC) independently of *H. pylori*, which are presented in later articles (Iijima K, Kanno T, Koike T, Shimosegawa T. *Helicobacter pylori*-negative, non-steroidal anti-inflammatory drug: negative idiopathic ulcers in Asia. World J Gastroenterol 2014; 20: 706-713; Lamb A, Chen LF. Role of the *Helicobacter pylori*-induced inflammatory response in the development of gastric cancer. J Cell Biochem 2013; 114: 491-497; Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet 2009; 374: 1449-1461; Tsimmerman YaS. [Critical analysis of the *Helicobacter pylori*-infection leading role in the development of gastroduodenal diseases]. Clinical pharmacology and therapy 2019; 28: 19-27).

The authors in no way detract from the value of the works indicated by the reviewer, but it should be noted that the works listed by the reviewer were written during the period of "fascination" with the pathogenic properties of *H. pylori* and almost in the absence of data regarding the potentially positive effect of the bacterium on the human body. Taking this into account, the authors review the data of more recent **meta-analyses** on the relationship of *H. pylori* and the development of a number of extra-gastric pathologies (Wang ZW, Li Y, Huang LY, Guan QK, Xu DW, Zhou WK, Zhang XZ. *Helicobacter pylori* infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. J Neurol 2012; 259: 2527-2537; Yu M, Zhang R, Ni P, Chen S, Duan G. *Helicobacter pylori* Infection and Psoriasis: A Systematic Review and Meta-Analysis. Medicina (Kaunas) 2019; 55: 645). In addition, in their review, the authors focus on the **meta-analysis** of Zhao *et al.* (Zhao Y, Li Y, Hu J, Wang X, Ren M, Lu G, Lu X, Zhang D, He S. The Effect of *Helicobacter pylori* Eradication in Patients with Gastroesophageal Reflux Disease: A Meta-Analysis of Randomized Controlled Studies. Dig Dis 2020; 38: 261-268) and **a multicenter randomized trial** of Xue *et al.* (Xue Y, Zhou LY, Lin SR, Hou XH, Li ZS, Chen MH, Yan XE, Meng LM, Zhang J, Lu JJ. Effect of Helicobacter pylori eradication on reflux esophagitis therapy: a multi-center randomized control study. *Chin Med J (Engl)* 2015; **128**: 995-999) on the effect of eradication therapy in HP-positive patients on the course of gastroesophageal reflux disease. The authors assume that the results of these articles indicate both the pathogenicity of *H. pylori* and its potentially positive effect on the human body.

3) The review lacks data on *H. pylori* infection and risk of developing autoimmune diseases particularly systemic lupus erythematosus (SLE). The manuscript presents data on the effect of *H. pylori* on the development of gastric mucosal lesions in patients with systemic lupus erythematosus and antiphospholipid syndrome, and it **does not consider** data on the persistence of *H. pylori* in connection with the risk of developing autoimmune diseases. The described data demonstrate that the lesions of the gastric mucosa, which is presented in these diseases, do not have a clear and reliable relationship with the detection of *H. pylori*, but there is a significant

relationship with the intake of glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAID) and anticoagulants.

4) Discussion of the relationships between *H. pylori* persistence and changes in microbiota composition is the subject of a separate large review, which is not the purpose of this paper. In the last decades, there has been an active discussion in the academic literature regarding the relationship between HP and gastric microbiota. In addition, the submitted manuscript has a large volume. Therefore, the authors considered it possible not to include such an important and overly extensive section in this review. We hope for the reviewer's understanding on this issue and expect him to agree with this argument.

5) In their work, the authors indicate that CagA -, VacA-positive strains of *H. pylori* play an important role in damage of the gastric and duodenal mucosa. But at the same time, the authors considered it important to attract the attention of gastroenterologists and the scientific community to the appearance of an increasing number of publications on the potential positive effects of various HP strains on the development of asthma (especially in children), inflammatory bowel diseases (IBD) and gastroesophageal reflux disease (GERD). The section "***H. pylori* and asthma**" presents papers discussing the inverse relationship of pathogenic strains of *H. pylori* (CagA-, VacA-positive strains) and asthma (Elias N, Nasrallah E, Khoury C, Mansour B, Abu Zuher L, Asato V, Muhsen K. Associations of Helicobacter pylori seropositivity and gastric inflammation with pediatric asthma [published online ahead of print, 2020 Jun 16]. Pediatr Pulmonol. 2020;10.1002/ppul.24905; Oertli M, Noben M, Engler DB, Semper RP, Reuter S, Maxeiner J, Gerhard M, Taube C, Müller A. Helicobacter pylori γ-glutamyl transpeptidase and vacuolating cytotoxin promote gastric persistence and immune tolerance. Proc Natl Acad Sci USA 2013; 110: 3047-3052).

Response to the reviewer ID – 02446277.

The authors express their sincere and deep gratitude to the reviewer for the careful study of the submitted manuscript and its high assessment. We are pleased that the reviewer briefly and accurately reflected in the review the essence of the work and the intention of the authors. All suggestions of the reviewer were taken into account, and the necessary corrections were made to the text of the manuscript (highlighted in bright blue):

1) The prevalence of *Helicobacter* infection in Italy was presented in accordance with the original data of Luzza *et al.* (Luzza F, Suraci E, Larussa T, Leone I, Imeneo M. High exposure, spontaneous clearance, and low incidence of active *Helicobacter pylori* infection: the Sorbo San Basile study. Helicobacter 2014; 19: 296 -305) and depending on the methods used to detect *H. pylori*.

2) In his work, Hooi *et al.* (Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis) present data from a number of publications (meta-analysis) on the prevalence of *H. pylori* in different countries and in different regions of these countries, apparently without taking into account the methods of its detection. This may be the reason for the low prevalence of *H. pylori* in these countries, which differs from the data presented in Luzza *et al.* This is why the authors presented the work of Mentis *et al.* according to the prevalence of *H. pylori* in Italy and Poland and in connection with the reviewer's comment, added data from Luzza *et al.*

The authors express their special sincere gratitude to the reviewer for the comments made and the exact indication of inaccuracies made in the manuscript.

3) Grammatic error in sentence on page 2 is corrected: "The re-assessment of the data available on HP infection is important to answer the question of whether it is necessary to create a program of mass *H. pylori* eradication or to apply a more personalized approach to treating patients with HP-associated gastrointestinal diseases and to perform eradication therapy".

4) The sentence on page 8 is revised: "Due to the activation of the Th1 cellular component of the immune system, the Th2 cellular pathway for differentiation of immature lymphocytes is not believed to play a considerable role in the immune response". We hope that it has become clearer.

Once again, we express our gratitude to the reviewer for his comments aimed at improving the manuscript.

Response to the reviewer ID – 02462321.

The authors express their gratitude for the detailed analysis of the manuscript and the comments made. Response to the reviewer in accordance with the comments:

1) The authors agree with the reviewer that methods for detecting *H. pylori* are important for determining the incidence of infection in different countries and regions. The description of these methods was not part of the aim of this review. However, taking into account the reviewer's wishes, data on the significance of *H. pylori* detection by different methods for assessing the incidence of infection in Italy have been added to the text (Luzza F, Suraci E, Larussa T, Leone I, Imeneo M. High exposure, spontaneous clearance, and low incidence of active *Helicobacter pylori* infection: the Sorbo San Basile study. *Helicobacter* 2014; 19: 296 – 305). But respiratory, serological and histological tests, unfortunately, do not allow us to determine whether the infection is primary or there was a re-infection after eradication. To do this, you should perform genetic studies, which are carried out most often for scientific purposes (see the link **Reshetnyak**

VI, Reshetnyak TM. Significance of dormant forms of *Helicobacter pylori* in ulcerogenesis. *World J Gastroenterol* 2017; **23**: 4867- 4878).

2) The authors, as well as the reviewer, do not consider that "…colonizing more than half of the world population is not, in its own right, an argument against its pathogenicity". The authors only emphasize that among the significant number of infected people in the world, there is a low percentage of those suffering from peptic ulcer disease (1%-10%) and those who develop gastric cancer.

3) The authors do not deny the pathogenic role of *H. pylori* and present in the review the mechanisms of Helicobacter's participation in the development of both peptic ulcer disease (PUD) and gastric cancer (GC) considered in the literature. However, it is not entirely clear why a decrease (by about 10%) in the incidence of gastric cancer after *H. pylori* eradication can be considered as its pathogenic factor, and an "alarming increase" in the incidence of asthma, inflammatory bowel diseases (IBD), gastroesophageal reflux disease (GERD), and etc. after eradication (by the same 10%) cannot be considered as a positive role? The data presented in the review indicate that the **presence** (rather than the absence) of *H. pylori* is likely to have a positive effect (which does not contradict Koch's postulate). At the same time, environmental factors, alimentary and social factors can affect both the development of asthma, IBD, GERD, and the development of GC and PUD. It is the contradictions that the authors of the review pay attention to, without detracting from the significance of the scientific data of both views.

4) When writing the manuscript, the authors touched on general information about *H. pylori*, considering that with them the manuscript will look more complete. At the same time, the editorial office of the journal usually does not limit the volume of such reviews. With this in mind, we hope that the reviewer will not insist on shortening these chapters of the review. We thank the reviewer in advance for this.

5) There are many works devoted to the importance of *H. pylori* in the development of PUD and GC in the scientific literature, and doctors are well acquainted with them. Therefore, the authors also paid little attention to the implication of *H. pylori* in extra-gastric diseases. Immediately after the discovery of *H. pylori*, considerable attention was paid to the pathogenic properties of this bacterium in the development of PUD and GC. But in recent years, more and more often *H. pylori* is being presented as a pathogen in extra-gastric diseases. Time will tell how justified this is. But we probably should know about it. Since the review focuses on the pathogenic properties of *H. pylori* and its positive effects on the human body, the authors briefly touched on this issue in their review.

6) The authors agree with the reviewer on the importance of "a balance between host defense mechanisms and pathogenic microbial aggression". At the same time, it is well known that the

symbiotic properties of a microorganism imply the occurrence of this microorganism in the population and its ability to exhibit pathogenic properties: the more often a microorganism is found among healthy people, the greater is the probability of its symbiotic relationship with the host organism and the more severe adverse changes in the state of the macroorganism are necessary for the realization of the pathogenic capabilities of the bacterium. The intestinal microflora is a confirmation of this thesis. Certain conditions, mainly associated with changes in the reactivity of the host immune system, can lead to changes in the symbiotic properties and the manifestation of conditionally pathogenic properties of this microflora.

7) The authors in no way deny the etiological role of *H. pylori* in the development of PUD. But at the same time, the authors urge to consider the infectious theory in combination with other causal factors (genetic, hereditary, etc.) of peptic ulcer disease. From a clinical point of view, it is important to assess the frequency of development of PUD in HP-positive and HP-negative patients, which is somehow related to the frequency of detection of *H. pylori* in patients without symptoms of gastrointestinal pathology. As the reviewer points out, the paper by Sidorenko *et al*. published in 2002, when there was no mass eradication trend in the treatment of patients with PUD. Therefore, the data of the article by Araújo *et al.* only confirm the fact of high occurrence of *H. pylori* among representatives of a healthy population (especially when compared with the detection of *H. pylori* in patients with a confirmed diagnosis of PUD).

8) The authors do not deny the pathogenic role of *H. pylori* in patients **prone to** the development of PUD. At the same time, the authors emphasize the fact that in patients with PUD, along with the pathogenic properties of *H. pylori*, it is necessary to take into account the impact of other etiological factors that have a damaging effect on the mucous membrane of the stomach and duodenum (genetic, hereditary, psychoemotional stress, dysfunctional disorders of the autonomic nervous system, eating habits, smoking, excessive alcohol consumption, use of steroid and non-steroidal anti-inflammatory drugs). In this case, the pathogenetic paradigm of PUD is a combination of the effects of pathogenic strains of *H. pylori* in conjunction with the action of other factors contributing to the development of PUD. The authors tend to believe that it is the presence of a set of factors that contributes to the manifestation of pathogenic properties of *H. pylori.*

9) In their review, the authors used the term “beneficial protective role”, based on the works available in the literature (Karakullukcu A, Tokman HB, Nepesov S, Demirci M, Saribas S, Vehid S, Caliskan R, Taner Z, Cokugras H, Ziver T, Demiryas S, Kocazeybek B. **The protective role** of *Helicobacter pylori* neutrophil-activating protein in childhood asthma. Allergol Immunopathol (Madr) 2017;45(6): 521-527; Ranjbar R, Karampoor S, Jalilian FA**. The protective effect** of *Helicobacter Pylori* infection on the susceptibility of multiple sclerosis. J

Neuroimmunol. 2019 15; 337: 577069; Lankarani KB, Honarvar B, Athari SS. The Mechanisms Underlying ***Helicobacter Pylori*-Mediated Protection** against Allergic Asthma. Tanaffos. 2017; 16(4): 251-259). But taking into account the reviewer's comments, the authors changed the name of the section and put the word "protective" in quotation marks (highlighted in purple in the text), implying an inverse correlation established in epidemiological studies between the detection of *H. pylori* and the development of asthma. The authors take into account that statistical correlations are used, as a rule, to represent the pathogenic properties of a microorganism. At the same time, the statistical principle of inverse correlation, apparently, can also be used to study the beneficial effect of a microorganism on the human body (by analogy with the study of the efficiency of treatment and the lack of efficiency of treatment).

The authors also pay attention to the presence in the scientific literature of studies explaining the mechanisms of anti-atopic action of *H. pylori* (Oertli M, Noben M, Engler DB, Semper RP, Reuter S, Maxeiner J, Gerhard M, Taube C, Müller A. Helicobacter pylori γ-glutamyl transpeptidase and vacuolating cytotoxin promote gastric persistence and immune tolerance. Proc Natl Acad Sci USA 2013; 110: 3047-3052).

The authors agree with the reviewer's opinion that the word "defense" is not quite correct for use in this context, so we have changed this sentence as follows: "*H. pylori* persistence may be supposed to be a potentially beneficial factor against the development of IBD" (highlighted in purple in the text).

It should be taken into account that up to the present time both ulcerogenesis and carcinogenesis are considered to be multifactorial processes with ambiguous dominance of etiological factors. That means, these pathological processes can develop under the influence of a number of etiological factors (as already mentioned above, in the process of ulcerogenesis, important aspects are genetic, hereditary factors, psychoemotional stress, dysfunctional disorders of the autonomic nervous system, eating habits, smoking, excessive alcohol consumption, the use of steroid and non-steroidal anti-inflammatory drugs, anticoagulant therapy). According to various authors, the predominant role of each of these factors is controversial. In our opinion, the persistence of *H. pylori* in the gastric mucosa is a triggering factor, but the disease will develop only under the combined action of a number of the above conditions.

Since the authors do not deny the importance of *H. pylori* eradication therapy **in the presence** of HP-associated PUD, this work in no way contradicts the principles of the WHO. The authors only advocate a personalized approach to conduct eradication therapy in the detection of *H. pylori* without etiopathogenetic factors for the development of PUD.

Thank you very much for the opportunity to revise our manuscript. We appreciate the careful

review and constructive suggestions of reviewers.

On behalf of all the authors of the article, please accept our congratulations on the coming New Year 2021. Best wishes for a happy New Year!

Sincerely yours,

Vasiliy Ivanovich RESHETNYAK, MD, PhD, DSc of medicine, professor.

Department of propaedeutic of internal diseases and gastroenterology, A.I. Yevdokimov Moscow State University of Medicine and Dentistry. Delegatskaya St., 20, building 1, 127473, Moscow, Russian Federation.

Telephone: +7-495-6096700

Fax: +7-495-6812229

E-mail：vasiliy.reshetnyak@yandex.ru