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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 61406

Title: Helicobacter pylori: commensal, symbiont or pathogen?

Reviewer's code: 04913316

Position: Peer Reviewer

Academic degree: AGAF, MD, PhD

Professional title: Full Professor, Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Russia

Manuscript submission date: 2020-12-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-12-05 16:58

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This is an interesting review on *H. pylori* which in my opinion could be improved

COMMENTS 1) English needs a thorough revision by a native English speaking person

2) In the paragraph on transmission, the Authors should quote the article by Sgambato et al highlighting the transmission between sexual partners (Prevalence of *Helicobacter pylori* transmission in sexual partners of *H. pylori*-infected subjects: role of gastroesophageal reflux. Sgambato D et al. *United Eur Gastroenterol J* 2018; 6:1470-1476).

3) In the section on *H. pylori* virulence factors the Authors should discuss the mechanisms whereby *H. pylori* may affect gastric carcinogenesis (*Helicobacter pylori*-related gastric carcinogenesis - implications for chemoprevention. M. Romano, et al V. *Nat Clin Pract Gastroenterol Hepatol* (now *Nat Rev Gastroenterol Hepatol*) 3: 622-632, 2006) (*Helicobacter pylori* gamma-glutamyl transpeptidase and its pathogenic role. V Ricci, et al. *World J Gastroenterol* 20: 630-638, 2014)



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 61406

Title: Helicobacter pylori: commensal, symbiont or pathogen?

Reviewer's code: 03818597

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor, Instructor, Teaching Assistant

Reviewer's Country/Territory: Iran

Author's Country/Territory: Russia

Manuscript submission date: 2020-12-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-12-12 11:51

Reviewer performed review: 2020-12-12 18:03

Review time: 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The manuscript has interesting topic as well as well written but I have some concerns: - in my opinion the primary paragraphs are unnecessary for this study such as “Basic facts”, “Epidemiology and routes of transmission”. - there is several evidences about the impact of eradication of H. pylori and reducing the risk of recurrence ulcers or secondary gastric cancer ([https://doi.org/10.1016/S0140-6736\(02\)07273-2](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/>) ; the authors should be suggested to these documents and have extent with the sentences about: Why your results are different with previous publications. - The authors could be use from several tables to summarized the evidences. - The authors discussed about the controversial evidences about H. pylori infection and risk of develop to autoimmune diseases particularly Systemic lupus erythematosus (SLE); I recommend that the authors can be discuss about the impact of H. pylori (type of genome and virulence factor) and eradication of H. pylori infection on autoimmune disease (You can preferably use the available meta-analyses). - Please discuss about the impact of H. pylori in alternation of microbiota and risk of develop to H. pylori-related gastrointestinal diseases particularly peptic ulcer and gastric adenocarcinoma. - The authors try to introduce the numerous evidence for beneficial effects of H. pylori infection in decreasing risk of develop to asthma, inflammatory bowel diseases (IBD), or gastroesophageal reflux disease (GERD) but it is conflicting; it has been suggested that cagA/vacA negative H. pylori (non-virulent H. pylori strains) has beneficial effects compared that cagA or vacAs1m1 H. pylori strains (more-virulent H. pylori strains), Therefore, I recommend to discuss about the impact of cagA or vacA s1/m1 H. pylori strains and risk of asthma, inflammatory bowel diseases (IBD), and gastroesophageal reflux disease (GERD) that does infection with more virulent strains (cagA/vacA s1m1 expressing strains) also reduce the risk of



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these diseases? And also provide literatures about the increasing risk of develop to asthma, inflammatory bowel diseases (IBD), or gastroesophageal reflux disease (GERD) when H. pylori infection eradicated? Good luck



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 61406

Title: Helicobacter pylori: commensal, symbiont or pathogen?

Reviewer's code: 02462321

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Chief Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Russia

Manuscript submission date: 2020-12-05

Reviewer chosen by: Lian-Sheng Ma

Reviewer accepted review: 2020-12-06 10:03

Reviewer performed review: 2020-12-14 00:54

Review time: 7 Days and 14 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

WJG Comments H. pylori: commensal, symbiont or pathogen? By Vasily Ivanovich Reshetnyak et al The AA consider the published data on Hp and focus major attention on its role as a commensal or symbiont, as opposed to its pathogenic activity in Human Beings. They assume that the available data discussing the presence or absence of the bacterium point toward an apparent ambiguity of the problem. They therefore cast serious doubt on the program of mass Hp eradication and dispute against the test and treat approach. Major general Comments 1) The AA do not take into account the modality of "Hp positivity": serology, histology or urea breath test? This obviously may make a difference: is it a past or a current infection that affects a given physiological or pathological condition? 2) The observation that Hp has been colonizing more than half of the world population (along with all the other local epidemiological figures) is not, in its own, an argument against its pathogenicity. A bacterial agent cannot be considered "safe" or even "useful" and then symbiont just because it affects half of the world population. For it to be accepted is mandatory to show a "positive" beneficial activity. Its absence or its negation is clearly not enough. 3)The coincidence of the gradual decline of Hp infection and gastric cancer (thanks to treatment), with an alarming increase in asthma (that can be due more likely to environmental factors) and with the escalation of esophageal diseases (GERD, Barrett' esophagus, and adenocarcinoma of the esophagus, that can be due to alimentary and social costumes, among other factors) does not signifies, in no way, a protective role of Hp on these diseases. In other words, if it is necessary for a given pathogen to comply with the Kock postulate to demonstrate its causative role, it is wrong to give a "protection" significance to its absence. This is a mistake to be avoid, even if can be present in too many scientific Journals. It would cause to go without the benefits derived from the eradication of Hp. 4)

Considering the aim of the article, the section devoted to the "General characteristics



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of Hp” and “Pathogenic properties of Hp” are exceedingly detailed, too long and useless: they need to be more concise. 5) The implication of Hp in the pathogenesis of extra-gastric diseases is undoubtedly controversial, but, again, the AA spend too much room to them. 6) The argument of “rare development of symptoms (and pathologies) notwithstanding the high prevalence of Hp in the population” is not, in its own, a motivation in favor of its commensal nature: as it is well-known the balance between host defense mechanisms and pathogenic aggression is crucial in the development of the disease. 7) The similar detection rate of Hp in PUD and in general population cannot be assumed as an evidence of its lack of pathogenicity. To support this point of view the AA quote the publications of Sidorenko and of Araujo, respectively published in 2002 and 2014, when the epidemiology of Hp was largely modified thanks to the extensive eradication treatment adopted so far. 8) The multiplicity of the causative agents on PUD, does not subtract any pathogenic responsibility to Hp. 9) The section titles “Beneficial protective role of Hp in asthma,...and IBD” cannot be accepted: they can pass a wrong message. The AA can only note an epidemiological inverse correlation, that, again, does not implies causative responsibility. Many other factors are involved. The defense mechanism of Hp in IBD needs yet to be demonstrated, if any. The AA cannot use the term “defense”. So been so, the extensive epidemiological data on these inverse correlation are in excess. In conclusion the presented data do not support a clear ambiguity of the Hp in the process of peptic ulceration and gastric carcinogenesis. This message is against the position and guidelines of WHO, and, in the present form, passes dangerous messages to the clinicians. The AA must make a major conceptual revision of the manuscript, with a different, more balanced approach and critical interpretation of the current literature, for it to be accepted.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 61406

Title: Helicobacter pylori: commensal, symbiont or pathogen?

Reviewer's code: 02446277

Position: Peer Reviewer

Academic degree: MS, PhD

Professional title: Academic Research, Research Assistant Professor, Senior Scientist

Reviewer's Country/Territory: Romania

Author's Country/Territory: Russia

Manuscript submission date: 2020-12-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-12-08 07:36

Reviewer performed review: 2020-12-14 11:12

Review time: 6 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The manuscript submitted by Reshetnyak V.I. et al., approaches a very interesting hypothesis of considering *H. pylori* as part of human microbiome as a commensal or even a symbiont. The authors specified both the idea of pathogenicity of *H. pylori* and arguments in support of the opportunistic pathogen hypothesis. The authors present evidences that the decline in *H. pylori* prevalence or its eradication as a result of antibiotic treatment, had various consequences like: an alarming increase in asthma, a potential increase in the susceptibility to diarrheal diseases, or an escalation of esophageal diseases including esophageal cancers. The ideas presented in this regard are extensively developed with examples from the literature. The manuscript has a rich bibliography. It is well organized. The flow is logical and concise. Major comments: 1.

I do not agree with the positivity rate for *H. pylori* in Italy. In the article cited Mentis et al [19], the authors made a mistake. Mentis cited incorrectly Francesco Luzzza's article (Luzzza 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). Respective article specifies: "Of 518 subjects who were evaluated by both UBT and serology, 310 (59.8%) were UBT positive, 479 (92.4%) VacA positive, and 369 (71.2%) CagA positive". Moreover, in the cited article by Hooi JKY et al. *Gastroenterology* 2017(21), over percentages are presented: for example Italy 56.2% and Poland 66.6%. Minor comments: - grammar problem page 2: "...to apply a more personalized approach to treating patients with HP-associated gastrointestinal diseases and to performing eradication therapy." The verb should be corrected to appropriate form - unclear phrase (page 8): "Due to the activation of the Th1 cellular component of the Th2 immune system,..."



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 61406

Title: Helicobacter pylori: commensal, symbiont or pathogen?

Reviewer's code: 04913316

Position: Peer Reviewer

Academic degree: AGAF, MD, PhD

Professional title: Full Professor, Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Russia

Manuscript submission date: 2020-12-05

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2020-12-29 06:20

Reviewer performed review: 2020-12-29 06:28

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The Authors addressed properly my comments



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 61406

Title: Helicobacter pylori: commensal, symbiont or pathogen?

Reviewer's code: 03818597

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor, Instructor, Teaching Assistant

Reviewer's Country/Territory: Iran

Author's Country/Territory: Russia

Manuscript submission date: 2020-12-05

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2020-12-29 04:56

Reviewer performed review: 2020-12-29 09:35

Review time: 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Well revised.