Title page:

Title: Not an easy road to generate an effective *Helicobacter pylori* vaccine

Running title: *H. pylori* and vaccine

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Author contributions: Amin TBA designed the research and analyzed the data and finally wrote the article.

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Sirs,

We have read with great interest paper by Meza *et al* entitled “ A novel design of a multi-antigenic, multistage and multi-epitope vaccine against *Helicobacter pylori*: An *in silico* approach ” published in Infection, Genetics and Evolution (1).

Unquestionably, following the frequently defeated antibiotic therapies of *Helicobacter pylori*, new alternatives should take into the account (2-4). Vaccination is a main option, especially for developing countries. Concerning the *H. pylori*, epitope-based vaccines are the novel approach to induce acceptable immunity and protection for infected individuals (5, 6). Meza *et al* reported their CTB-multiHp vaccine as the promising approach to be used in battle with the bacterium. However, there are major points which should be mentioned as constructive comments to improve the application of this new coming vaccine.

- The most important lacking concerning this proposed vaccine is about supportive clinical data including *in vivo* models. In the case of *H. pylori* we absolutely want promising findings indicating on therapeutic features of a vaccine. The bacterium causes a chronic infection which mostly lasts long life. Application of a vaccine against *H. pylori* needs certainty on its induced protection and effective immune response.
- Immune reactivity of epitope vaccines is the major challenge in this field of the research. Although in this study CTB was used as the immune adjuvant but no further safety assays are not presented accordingly to prove a primary claim. This sort of experiment is necessary before universal prescription of this product.
- Apart from authors who believe that immunological, physicochemical, and structural characteristics of this vaccine are well-prepared for the subjects, we strongly think about many left behind experiments before this straight conclusion.
- Since *H. pylori* infection mostly lasts for a long time and its related diseases outcomes can disclose only following this time period, authors should have presented their results promising after this follow-up system include what Zeng *et al* reported in *Lancet* (7).

Surely, this study can be a pilot for a future novel panel of vaccine design and application in developing countries at least.

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