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**Chinese *Helicobacter pylori* vaccine: solution for an old challenge?**

**Running title:** Successful vaccination against *H. pylori*

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is an important cause for gastric cancer in high risk individuals. *H. pylori* colonizes more than 50% of the world’s population and associated peptic ulcer disease and gastric malignancy have important public health implications. It has been classified as a class I carcinogen in 1994 by the World Health Organization. Clinicians are often prompted to eliminate the infection the moment it is detected. This also, unfortunately, led to reckless use of antibiotics and reports of increasing resistance are now worldwide. Each year, many of people die from gastric cancer; thus application of effective vaccine can reduce this relatively high mortality worldwide. *H. pylori* can be eliminated by antibiotics but efficacy is sharply decreasing. Moreover, current therapy is also expensive and with side effects. Vaccine may be the best solution to the above problem but there are many challenges in producing such an effective therapeutic vaccine. Recently, the Chinese group published in *Lancet*, a single-center, randomized, phase III study of an oral recombinant vaccine (Urease B subunit fused with heat-labile enterotoxin B derived from *Escherichia coli*) prescribed in the Chinese children (6-15 years) without a history of *H. pylori* infection. This review provides an insight into this new solution for an old challenge.

**Key words:** *Helicobacter pylori*; therapy; vaccine; antibiotics; resistance

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**Core tip:** *Helicobacter pylori* (*H. pylori*) remains the most prevalent gastric infection. One of the main questionable aspects of *H. pylori* is its high resistance to most of prescribed antibiotics and lack of useful vaccines. Vaccine may be the best solution to the above problem but there are many challenges in producing such an effective therapeutic vaccine. That will be ideal that Chinese vaccine removes the need for bicarbonate administration because of its adverse side effects. Taking together, it is the first time that such a protective *H. pylori* vaccine is introduced to the world for high risk individuals.

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**Introduction**

***It is time to stop Helicobacter pylori***

*Helicobacter pylori* (*H. pylori*) infects over half of the world’s population and associated peptic ulcer disease and gastric malignancy have important public health implications. Despite after two decades of antibiotics success, the primary problem still exists, and the reasons can be multifactorial[1-3]. Some *in-vivo* conditions favor the persistence of *H. pylori* in the stomach but others oppose, and the clinical outcomes can be dependent on a delicate balance between a harmless inflammation and a more severe kind[4]. Furthermore, we do not know the most effective eradication regime of *H. pylori*, as the following questions remained unsolved including the best duration of recommended regimens, best dosages and also the right combination of antibiotics[5-8]. Although *H. pylori* infection can be efficiently eradicated using antibiotics, at least, in some patients, there are now reports of antibiotic resistance worldwide (Table 1). Finding an effective vaccine is the answer if resistance continues to increase[9-12]. More than five international guidelines have been published that covers all aspects of *H. pylori* infection including diagnostic, treatment and also vaccine[13,14]. Following years of continuous clinical experiments and trials, the promising goal for an effective vaccine now seems feasible. In September 2015, a report published in Lancet by the Chinese group brings high hope on a highly effective vaccine that we have been waiting for[15]. If proven in further studies, then this groundbreaking finding will change management paradigm of *H. pylori* in the near future.

**A *H. pylori* vaccine that works, finally?**

Effective vaccine should not just reduce the incidence but also global prevalence of *H. pylori*. Furthermore, to prove its efficacy we need a longer period of study observation and with a greater number of study participants to conclude its reliability before it can be recommended into any healthcare systems. There have been considerable interests to develop such an effective *H. pylori* vaccine for a long time but many obstacles had hampered the development[16]. Many of the *H. pylori* virulence factors and also secreted proteins such as urease were used as recombinant proteins to produce a protective vaccine, but because these factors only induced weak forms of immunity and also lack of safety, therefore many projects were abandoned[13,17]. Therapeutic vaccines should be able to administer to both *H. pylori* positive children but also adults; although there is a potential risk for developing gastritis in susceptible patients[18,19]. In these susceptible patients, however, we can still recommend therapeutic vaccine; since it can reduce 1- risk of re-infection and 2- decrease treatment duration. The disappointment in vaccine development may tip following the Chinese *H. pylori* vaccine published in Lancet [15]. This was a single-center, randomized trial and a phase III study that examined an oral recombinant vaccine (based on Urease B subunit fused with heat-labile enterotoxin B derived from *Escherichia coli*) among the Chinese children (aged 6-15 years) without a prior history of *H. pylori* infection. In brief, after 12 mo of vaccination, 71% efficacy rate was observed, and this rate was around 55% after 3 years. Although seems effective in children, this study needs repeat among adults. Another limitation of this vaccine is that the authors found 20% of younger children were not protected from the infection. Notably, using better adjuvant in order to remove boosters for this vaccine may increase its popularity among clinicians for widespread prescription. Also it will be ideal that the Chinese vaccine removes the need for bicarbonate administration because of its adverse side effects. Taking together, it is the first time that such a protective *H. pylori* vaccine is introduced to the world for high risk individuals.

**What now after the Chinese vaccine?**

While the published results for the Chinese vaccine seems promising, but there are still barriers before it gains wide acceptance. Besides the limitations mentioned in above section, the vaccine needs a proper Phase-III clinical trials for other populations. Besides the Chinese vaccine, there are other novel developments in the pipeline. Currently, there is a lack in knowledge on exact molecular mechanisms that contributed to cellular immunity against *H. pylori*. The urease enzyme was the first recombinant protein used to provide an effective vaccine for *H. pylori* in animal models[20,21]. Recently, it has been established that regulatory T-cells are necessary to mount sufficient immune responses and this is important information for future development of a protective anti-*H. pylori* vaccine[22]. *H. pylori*-immunogenic antigens such as catalase, vacuolating cytotoxin (VacA), urease, cytotoxin-associated gene A (CagA), heat shock proteins and also neutrophil-activating protein (NAP) had been examined to see if they are potential candidate antigens for vaccine[23-27], but so far, the results have been inconclusive. Moreover, different mucosal routes such as sublingual, rectal and intranasal were being evaluated but results were inconsistent[27-30]. Recently, Chen *et al*[31] examined *oipA* DNA construct carried by the bacterium, Salmonella typhimurium as a therapeutic vaccine. The authors concluded that *H. pylori* virulence factors including OipA and NAP may seem to be the better candidates to induce effective immunity, at least in the mouse models, and we shall await more results.

**Conclusion**

Due to the relatively high rate of antibiotic therapy failure in recent years, we have to investigate more about novel vaccines on *H. pylori*. At last, Chinese group proposed a useful formulation with less side effects which can inspire more hopes for clinicians to think actually about *H. pylori* mass eradication worldwide.

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**Table 1 Worldwide report of increasing *Helicobacter pylori* antibiotic resistance**

|  |  |  |  |
| --- | --- | --- | --- |
| **Year** | **Eradication rate** | **Ref.** | **Antibiotics** |
| 2001 | 97% | Asaka *et al*[9] | Clarithromycin  Amoxicillin |
| 2014 | 61% | Chen *et al*[10] | Clarithromycin  Amoxicillin |
| 2014 | 55% | Kutluk *et al*[32] | Clarithromycin  Amoxicillin |
| 2013 | 76% | Sardarian *et al*[11] | Clarithromycin  Amoxicillin  tinidazole |
| 2013 | 80% | Zullo *et al*[33] | Clarithromycin  Amoxicillin  tinidazole |
| 2014 | 69% | Nishida *et al*[7] | Clarithromycin  Amoxicillin |
| 2011 | 87% | Greenberg *et al*[6] | Clarithromycin  Amoxicillin |
| 2014 | 98% | Sugimoto *et al*[12] | Metronidazole  Clarithromycin |
| 2013 | 38% | Nishizava *et al*[34] | Metronidazole  Amoxicillin Clarithromycin |