NIAID Workshop:
Development of a Standardized Human Challenge Model for *Helicobacter pylori*

November 30, 1999
Rockville, MD

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Conclusions
Questions Addressed at the Workshop

- **Are There Good Scientific and Clinical Reasons to Develop a Standardized Human Challenge Model for *H. pylori*?**
- **Are There Ethical Ways to Conduct a Human Challenge Model for *H. pylori*?**
- **What are the Criteria for Strain Selection?**
- **Which Clinical End-Points are Necessary to Access Vaccine Efficacy?**
- **How Should Volunteers be Monitored During the Trial?**

Conclusions

The results of the Workshop were presented and discussed at the NIAID Advisory Council meeting on February 18, 2000. It was the recommendation of the Council that the Institute should **not** pursue the volunteer challenge model at this time. Several factors entered into this decision including: 1) the lack of a compelling need for vaccination in the U.S. where the rate of natural infection is decreasing, 2) the lack of a clear vaccination strategy for the U.S. (who would be vaccinated?), 3) the fact that volunteers would be at risk of unsuccessful antibiotic eradication of the challenge strain for an infection with serious sequelae (ulcers and cancer) that may not be clinically diagnosed for many years after the trial, 4) the availability of animal models, which have not been thoroughly investigated as models for vaccine efficacy, and 5) the ability to measure vaccine efficacy by more conventional field trials. The possibility that infection with *H. pylori* may be a factor in protection against Gastroesopageal Reflux Disease (GERD) and esophageal cancer was also considered in the final recommendation. It was acknowledged that in certain endemic regions of the world, the benefit of an effective vaccine would be greater than in the U.S. and that the recommendation could change in the future if new information becomes available.

Questions Addressed at the Workshop

Are There Good Scientific and Clinical Reasons to Develop a Standardized Human Challenge Model for *H. pylori*?

The following summarizes the group's consensus:

a. Infection with *H. pylori* is a major cause of important diseases such as peptic ulcer disease, gastric adenocarcinoma, and primary gastric B-cell lymphoma.

b. A vaccine against *H. pylori* could be extremely important because there is a high probability that widespread use of current antimicrobial therapies will not be feasible, especially in developing countries, or even

among the very poor in the US — in part because of high cost, multiple side effects, the risk of reinfection and of emerging drug resistance.

c. Vaccines historically have been useful for disease prevention. It is important to consider establishing models for *H. pylori* vaccine development. The ultimate scientific goal would be field trials of likely vaccine candidates, but the present state of the knowledge does not provide a means for selecting such promising candidates.

d. As part of this effort and for other reasons, it is worthwhile to understand the correlates of protection and safety, as well as the pathogenesis of the disease.

e. Animal models (with the possible exception of monkeys) are not sufficient to address these fundamental issues.

f. A human challenge model can be developed for the main purpose of selecting optimal *H. pylori* vaccine candidates for field trials. Studies can be designed to provide important information on *H. pylori* immunity and pathogenesis.

Are There Ethical Ways to Conduct a Human Challenge Model for *H. pylori*?

The crux of this question is whether there is a positive balance between benefit and risk. The benefits of the challenge study to the subject are essentially zero. However, such studies can provide benefit to society at large. An *H. pylori* vaccine is potentially beneficial for humankind since it could help prevent diseases important in all parts of the world. Human challenge studies are a tool to expedite and facilitate vaccine development by providing a means for assessing vaccine efficacy in a small sample of subjects. Field trials would require more subjects followed for longer periods of time. However, field trials of other vaccine candidates have been done without the benefit of preliminary challenge studies.

Conversely, a small but real risk of administering virulent *H. pylori* to volunteers is the failure to eradicate the organism with antibiotics, which carries a risk of eventual development of serious disease. Additionally, there are the discomforts produced by the induced disease and the procedures (three endoscopies, some with biopsy, and antimicrobial therapy) that would form part of the study protocol. Informed consent must describe adequately these discomforts and risks. It is recommended that initial research protocols include the systematic measurement of discomfort or suffering experienced by volunteers in order to be able to assess the impact and safety of the challenge model. This assessment must be considered in a decision to proceed with additional studies using the model.

A summary of the risk-benefit analysis is as follows:

a. Volunteer challenge studies can provide important benefits to society.

b. Three risks, which can be minimized by carefully designed trials, distinguish *H. pylori* challenge trials from previous challenge models:
    1. The potential for long-term sequelae
    2. The potential for transmission to community contacts
    3. The need for complex antibiotic therapy and its potential to fail to eradicate the experimental infection.

c. Discomforts from the induced infection or protocol procedures are real and should be documented. Informed consent should include adequate description of risks and discomforts.

d. These risks can be reduced by a series of considerations related to study subject (host) and study design issues specific to *H. pylori* challenge. Relevant considerations raised at the meeting include the following:

Host factors

1. Previously healthy host
2. No added risks for *H. pylori*-associated diseases
3. Normal endoscopy and gastric histology prior to challenge
4. Not pregnant or lactating or intending to become pregnant in next 12 months
5. No intolerance (including allergy) to the agents to be used for treatment

Study design factors

1. No substantial occupational or household contact of subject with young children
2. Informed consent that clearly defines risks and benefits
3. The liability coverage available to the subject must be described
4. Adequate follow-up to ensure eradication and significant improvement in any challenge strain-induced gastric histopathologic changes
5. Follow-up of household contacts for related symptoms

What are the Criteria for Strain Selection?

The group divided the criteria into those characteristics that are necessary and those that are useful.

a. **Necessary Characteristics of the Cchallenge Strain**

1. Strain susceptibility to the first line and alternative antibiotics to be used for eradication, and the forward mutation rate defined
2. Freely available to all investigators in the field
3. Sufficient characterization including DNA fingerprinting, antigenic features, plasmid content
4. Minimally passaged in vitro, passage history documented, and inoculum produced under GLP or GMP
5. The donor of the strain should have no communicable diseases (e.g. HIV, Hepatitis B or C, syphilis) and should have no significant gastric histopathology

b. **Useful Characteristics of the Challenge Strain**

1. The strain should be shown to be susceptible to antibiotics in the donor; the donor should have been successfully eradicated
2. The strain can colonize animals and cross-protect against infections

A specific question that was vigorously debated concerns the genotype of the challenge strain. *H. pylori* strains that are *cagA+* are more highly associated with disease outcomes, and thus risk to the participants in the trials. However, these are the most important strains for a vaccine to

prevent human colonization, and a vaccine that prevented *cagA*- strains but not *cagA*+ strains would not be considered very useful. In addition, there is evidence that *cagA*+ strains are more susceptible to eradication therapies than *cagA*- strains.

With these considerations in mind, the conferees recommend that initial studies be done with a *cagA*- strain, to develop a body of safety data and to refine the study design. A *cagA*+ strain also would be selected and used for a second round of challenge studies with the knowledge that vaccine strategies must be successful at preventing infection with *cagA*+ strains.

Which Clinical End-Points are Necessary to Access Vaccine Efficacy?

Three different potential markers of vaccine efficacy were discussed:

a. **Symptoms**. Symptoms such as dyspepsia or abdominal pain are not specific for *H. pylori*, nor sufficiently sensitive to reliably detect its presence. Although volunteers would be monitored for symptoms, these would not be an end-point.

b. **Eradication of *H. pylori***. The prevention of persistent colonization after challenge would be a standard means for assessing whether an *H. pylori* vaccine was effective. An alternative proposed is "partial prevention" in which colonization is not prevented, but bacterial density is substantially lower than in the absence of vaccination. Such an effect could conceivably reduce the risk of disease.

c. **Absence of gastritis.** The presence of *H. pylori* in the stomach nearly universally induces a tissue response, called chronic gastritis. One end-point is the histologic evaluation of gastric tissue for the presence of gastritis.

How Should Volunteers be Monitored During the Trial?

If a challenge model was to be considered ethical, the conferees would then suggest that the time course of experiments illustrated in **Figure 1** be used. Before being enrolled in the study, each volunteer would be subjected to an esophago-gastro-duodenoscopy with mucosal biopsies (histology and culture) to rule out current *H. pylori* infection and presence of pathological lesions.

Following challenge, patients would be assessed for symptoms, immune response, and colonization by *H. pylori* using C-13 urea breath test. Just prior to initiation of triple therapy with a regimen of antimicrobials recommended by the FDA (approximately 1 month following challenge), endoscopy will be performed to assess histology, *H. pylori* presence and quantity, and local immune responses. Following treatment, the volunteers would be assessed with a reliable non-invasive test such as the urea breath test and/or stool antigen detection about one month after completion of therapy. In volunteers whose tests are positive, there would be immediate endoscopy with biopsy to determine histology and culturing of *H. pylori* to determine susceptibility. Recovered *H. pylori* will also be DNA fingerprinted (or gastric juice will be used for specific PCR amplification and sequencing) to determine if the recovered or persistent strain is of the same lineage as that used for infection. After susceptibility of the isolate is determined, the volunteer would be re-treated, and then reassessed.

For each volunteer whose tests are negative one month after treatment, a late evaluation of status is planned. A late endoscopy is planned at least 6 months after therapy to ensure eradication of the organism and restoration of the gastric mucosa to normal.

The type of schema used in *H. pylori* challenge models could be expanded for use in vaccine trial models **(Figure 2).** From the time of challenge, the conduct of the vaccine trial would closely parallel or be identical to the challenge model. The difference is that after the first endoscopy, the volunteers would be randomized to immunization and control arms. Following the immunization schedule, the challenge then would be given, as above.

Figure 1

Schematic of the challenge model

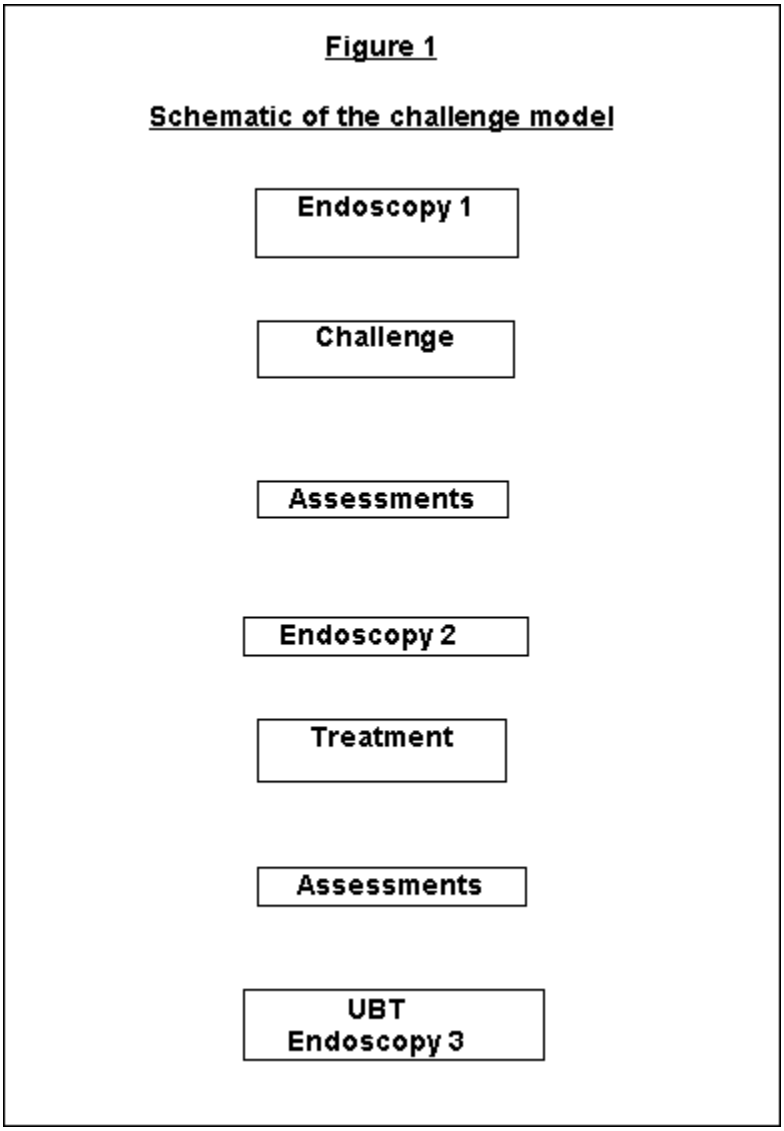

Figure 2

Schematic of the *H. pylori* vaccine trial model