Highly motile, Gram negative bacteria

Infects the mucus layer lining the stomach

An estimated 50% of the World’s population is infected

Infection typically starts in childhood

If untreated, most *H. pylori* infections remain for life

~15% of those infected are thought to develop an associated pathology

Route of transmission is controversial

Evidence suggests oral-oral is perhaps the most common route

Vertical transmission – especially mother-child
Where *H. pylori* infection is a cause of disease:

- Gastric ulcers
- Duodenal ulcers
- Gastric MALT lymphoma
- Gastric adenocarcinoma

*H. pylori*-driven progression to gastric cancer

Immune thrombocytopenic purpura (ITP)

Decades

- Childhood
- Superficial gastritis
- Atrophic gastritis
- Metaplasia
- Dysplasia
- Carcinoma

Potential period for intervention
Current treatments and their problems for preventing gastric cancer

*H. pylori* infections are currently treatable with combination antibiotics

Drug resistance a concern: “The prevalence of antimicrobial drug resistance is now so high that all patients infected with *H. pylori* should be considered as having resistant infections” (1)

Failure of antimicrobial therapy can lead to patient refusal of further treatment (2)

Patients typically present with gastric cancer without knowing they are infected: by this time eradication likely has little effect

Antibiotic treatment to protect against *H. pylori*-induced gastric cancer would therefore need to be performed at a population level to be effective

Potential issues include increasing antibiotic resistance in other diseases and not protecting against reinfection

Currently being trialled in China; treated 94,101 with 72.9% eradication (3)

Test and treat also used in some hospitals in China

(2) Yoon et al *J Gastroenterol and Hepatol* 2015; 30, 490.
(3) Pan et al *Gut* 10.1136/gutjnl-2015-309197
Pathogen, Diseases and Unmet Medical Need

Priority need(s) which would be met by a vaccine against *H. pylori*

**Primary need:**
Gastric adenocarcinoma

**Secondary benefit:**
Peptic ulcer disease (PUD); gastric and duodenal ulcers

- Still a major cause of morbidity and mortality in many countries
- Often uncertain how much PUD in developing countries is due to *H. pylori*
- Excessive NSAID use is also a major cause of PUD
Pathogen, Diseases and Unmet Medical Need

**Gastric adenocarcinoma**

5th most common cancer

952,000 new cases in 2012

(6.8% of all cancers)

3rd leading cause of cancer-related death

723,000 deaths in 2012

(8.8% of all cancers)

Rates about twice as high in males

Highest mortality rates in East Asia and Eastern Europe

~65-90% of cases are due to *Helicobacter pylori* infection
Pathogen, Diseases and Unmet Medical Need

Gastric adenocarcinoma incidence

Estimated age-standardised rates (World) per 100,000

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
Pathogen, Diseases and Unmet Medical Need

Gastric adenocarcinoma mortality

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Vaccine Development: Background

Mouse model: A widely used mouse model is available
Mice are not readily infected with *H. pylori*. A few mouse adapted strains have been developed
Mice only develop gastritis very slowly
Most vaccine studies in mice have used a single *H. pylori* strain

Rhesus macaques: In captivity macaques become naturally infected with *H. pylori*
A non-human primate model that provides a rigorous and relevant test for evaluating the efficacy of an *H. pylori* vaccine, before entering clinical trials

Human challenge strain of *H. pylori*:
Lacking major virulence factors
Susceptible to 4 antibiotics
Still induces gastritis
Vaccine Development: Background

1990’s – lots of excitement and investment
Mouse models of *H. pylori* infection were developed
OraVax patented urease-based *H. pylori* vaccines
CSL & UNSW patented therapeutic vaccination against *H. pylori*, licensed to AstraZeneca
AstraZeneca first to sequence *H. pylori*: patented >700 ORFs as putative vaccine antigens

Vaccines comprising many different
Antigens (i.e. urease, catalase, Hsp60, vacA, whole bacteria),
Adjuvants/delivery systems (i.e. CT, LT, alum, salmonella) and
Routes of delivery (nasal, oral, subcutaneous)
were shown to be protective in a mouse infection models

However
With improved assays, protection in mice was found to be only partial
Clinical trials were disappointing
# Vaccine Development: Background

Published Phase I trials of discontinued studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Company</th>
<th>Recipients</th>
<th>Vaccine</th>
<th>Route</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>OraVax</td>
<td>Infected</td>
<td>rUrease</td>
<td>Oral</td>
<td>Safe. No effect on infection.</td>
</tr>
<tr>
<td>1999</td>
<td>OraVax</td>
<td>Infected</td>
<td>rUrease + LT</td>
<td>Oral</td>
<td>Reduced <em>H. pylori</em> density in lowest antigen dose group. Diarrhoea.</td>
</tr>
<tr>
<td>2008</td>
<td>Max Planck</td>
<td>Uninfected, vaccinated then challenged</td>
<td><em>Salmonella</em> expressing rUrease</td>
<td>Oral</td>
<td>No protection. Some volunteers spontaneously cleared the challenged strain (unrelated to vaccine).</td>
</tr>
<tr>
<td>2008</td>
<td>Novartis</td>
<td>Uninfected</td>
<td>cagA, vacA &amp; NAP plus Alum</td>
<td>IM</td>
<td>Most recipients developed serum antibodies to all antigens. Showed T-cell memory responses.</td>
</tr>
</tbody>
</table>

Vaccine Development: Background

Over time investment fell and large biotech companies became disillusioned

Another factor?

Investment potentially affected by declining *H. pylori* levels in developed countries

*H. pylori* levels also now slowly declining in many developing nations, though this may be regional (1)

This has created a perception amongst many that *H. pylori* has/is disappearing

Still a very prevalent infection in many parts of the world

Recent data suggest infection rates may have stopped falling in Western countries (1, 2)

(1) Nagy *Gut Pathogens* 2016; 8, 8
(2) den Hoed *Helicobacter* 2011; 16, 405
## Vaccine Development: Background

### Current activity

<table>
<thead>
<tr>
<th>Company</th>
<th>Vaccine/technology</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EpiVax</td>
<td>HLA-binding epitopes</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Sichuan University</td>
<td>Urease epitope vaccine</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Southern Medical University</td>
<td>Lp220 epitope vaccine</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Helicovaxor®</td>
<td>Vibrio cholerae expressing H. pylori antigens</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Murdoch Childrens Research Institute</td>
<td>HtrA anti-inflammation vaccine</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Imevax</td>
<td>γ-glutamyl transpeptidase vaccine</td>
<td>About to enter Phase I</td>
</tr>
<tr>
<td>Wuhu Kangwei Biological technology</td>
<td>UreB/LTB fusion vaccine</td>
<td>Completed phase III. Discontinued?</td>
</tr>
</tbody>
</table>

*Note: Wuhu Kangwei Biological technology indicates that the company is working on a UreB/LTB fusion vaccine.*
Vaccine Development: Pipeline

Murdoch Childrens Research Institute; HtrA anti-gastritis vaccine

It is gastritis rather than *H. pylori per se* that drives cancer and PUD

The HtrA vaccine can prevent *H. pylori*-induced gastritis in mice

This avoids issues with the difficulties associated with eradicating infection

**Average *H. pylori* infected control mouse**

- Alum alone control: Metaplasia = 2.1 (1.0-2.5), Atrophy = 2.0 (1.0-2.0)

**Average therapeutically vaccinated mouse**

- HtrA+alum vaccine: Metaplasia = 0.0 (0.0-2.0), Atrophy = 0.0 (0.0-2.0)

Main problem: Attracting investment for the next stage
Vaccine Development: Pipeline

Imevax; γ-glutamyl transpeptidase (GGT) vaccine

GGT can suppress the T-cell response to *H. pylori* infection

A potential mechanism by which *H. pylori* evades immune clearance

This novel vaccine approach aims to neutralise *H. pylori* GGT, removing immunosuppressive activity and increasing immunity to other antigens

IMX101 comprises:

- GGT
- An outer membrane protein
- A mucosal adjuvant

Phase I clinical trials are scheduled to hopefully start the end of 2016

- Phase 1a: Uninfected volunteers
- Phase 1b: Infected volunteers
Vaccine Development: Pipeline

Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial

*Lancet* 2015; 386:1457-64

Ming Zeng*, Xu-Hu Mao*, Jing-Xin Li, Wen-De Tong, Bin Wang, Yi-Ju Zhang, Gang Guo, Zhi-Jing Zhao, Liang Li, De-Lin Wu, Dong-Shui Lu, Zhong-Ming Tan, Hao-Yu Liang, Chao Wu, Da-Han Li, Ping Luo, Hao Zeng, Wei-Jun Zhang, Jin-Yu Zhang, Bo-Tao Guo, Feng-Cai Zhu, Quan-Ming Zou

First phase III trial
First trial in children
First study of protection against natural acquisition
First demonstration of vaccine-mediated protection against *H. pylori*

Oral prophylactic vaccine:
Fusion protein of Urease B subunit and LT B subunit
Delivered 3x to children aged 6-14

After 1 year, 71.8% less acquisition:
Vaccine group: 14 out of 2,199 infected
Placebo group: 50 out of 2,204 infected

In a trial extension, some children were followed for 2 and 3 years:
Protection dropped to 55%.

Proof of concept: Vaccine-mediated protection against natural acquisition of *H. pylori*
Vaccine Development: Pipeline

Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial

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**Issues:**

Published in 2015, the trial was performed in 2005-2007

Recipients were fasted for 2 hours prior to vaccination

Relatively rapid waning of protection

As a **prophylactic** vaccine, 20% of prescreened children were excluded (infected)

Only some children will ever be infected.

If an estimate of 40% infection by age 18 is taken (for rural China based on recent figures):

71.8% reduction by prophylactic vaccination actually equates to only a 35.9% reduction in infection at the population level.
Assessment

Estimated chance of *H. pylori* vaccine emerging from pipeline

Currently slim due to:

- Few, if any advanced candidates
- Little current investment from big pharma; makes expensive late stage trials challenging

Cause for optimism:

- Recent publication of phase III proof of concept that vaccination can prevent natural *H. pylori* acquisition
- Analyses show a vaccine against *H. pylori* would be cost-effective even in USA where rates of infection and disease are lower (1)

Assessment

Potential role for WHO

Based on our personal experience of talking to a large number of potential investors and industry partners:

1) Increase education that *H. pylori* is still a major problem in many countries (with a very large market)

There is a very large gap in the knowledge of institutes and biotechnology companies from developed countries that commonly believe *H. pylori* is no longer a problem.
Assessment

Potential role for WHO

Based on our personal experience of talking to a large number of potential investors and industry partners:

2) Modify the perception that antibiotics are all that is required to prevent *H. pylori*-associated diseases

Antibiotics are an appropriate and effective tool to treat an individual known to be infected with *H. pylori*

However it needs to be recognised that antibiotics may not be the best option for a population level prevention of gastric cancer

(the antibiotic approach has its own major challenges and problems)
Assessment

Potential role for WHO

Based on our personal experience of planning long range strategies for *H. pylori* vaccine development:

3) A WHO collaborating centre in China (or similar) to either advise on, coordinate or act as a go-between for late stage clinical trial would be extremely useful.

Phase III trials (and possibly Phase II) would best be performed in a country with a high level of infection (such as China)

Such trials are very difficult to arrange without an appropriate and enthusiastic contact within the host country
Assessment

Potential role for WHO

4) Assess the contribution of \textit{H. pylori} to peptic ulcer disease in developing nations (especially East Asia)

Determine the level of mortality associated with this in these countries (relative contribution of \textit{H. pylori} and NSAID use)

Quality data on this important question is hard to find
Say you had an effective vaccine against *H. pylori*

**Decades**

- Childhood
- 50+

- Normal
- Superficial gastritis
- Atrophic gastritis
- Metaplasia
- Dysplasia
- Carcinoma

**Potential period for intervention**

**Prophylactic vaccine**

Great! …but

No benefits for 50+ years

– need to sell that

**Therapeutic vaccine**

Great! …but

Who and when would you vaccinate?
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