

Draft Report on Carcinogens Concept: *Helicobacter pylori* (Chronic Infection)

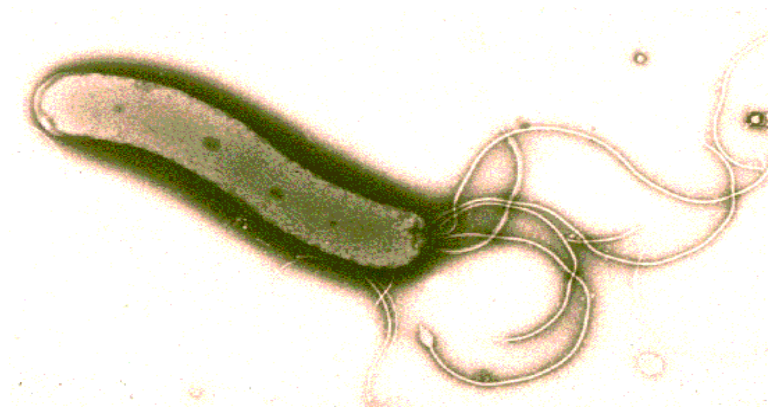
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***H. pylori* colonizes the stomach and causes peptic ulcers**

- Gram negative, multi-flagellated bacterium
- Colonizes the mucosal surface of the stomach usually lasting the lifetime of an individual
- Humans infected by multiple strains
 - Heterogeneous with respect to phenotype/genotype
- Genome codes for a number of virulence factors





H pylori is primarily spread by person-to-person contact

Risk factors for infections

- Infected family members, number of siblings
- Demographics: Age, geographical location, and ethnicity/race
- Socioeconomic status such as crowded living conditions, poor sanitation/hygiene
- Environmental (NHANES data): Well-water use among children, soil-related occupations among adults

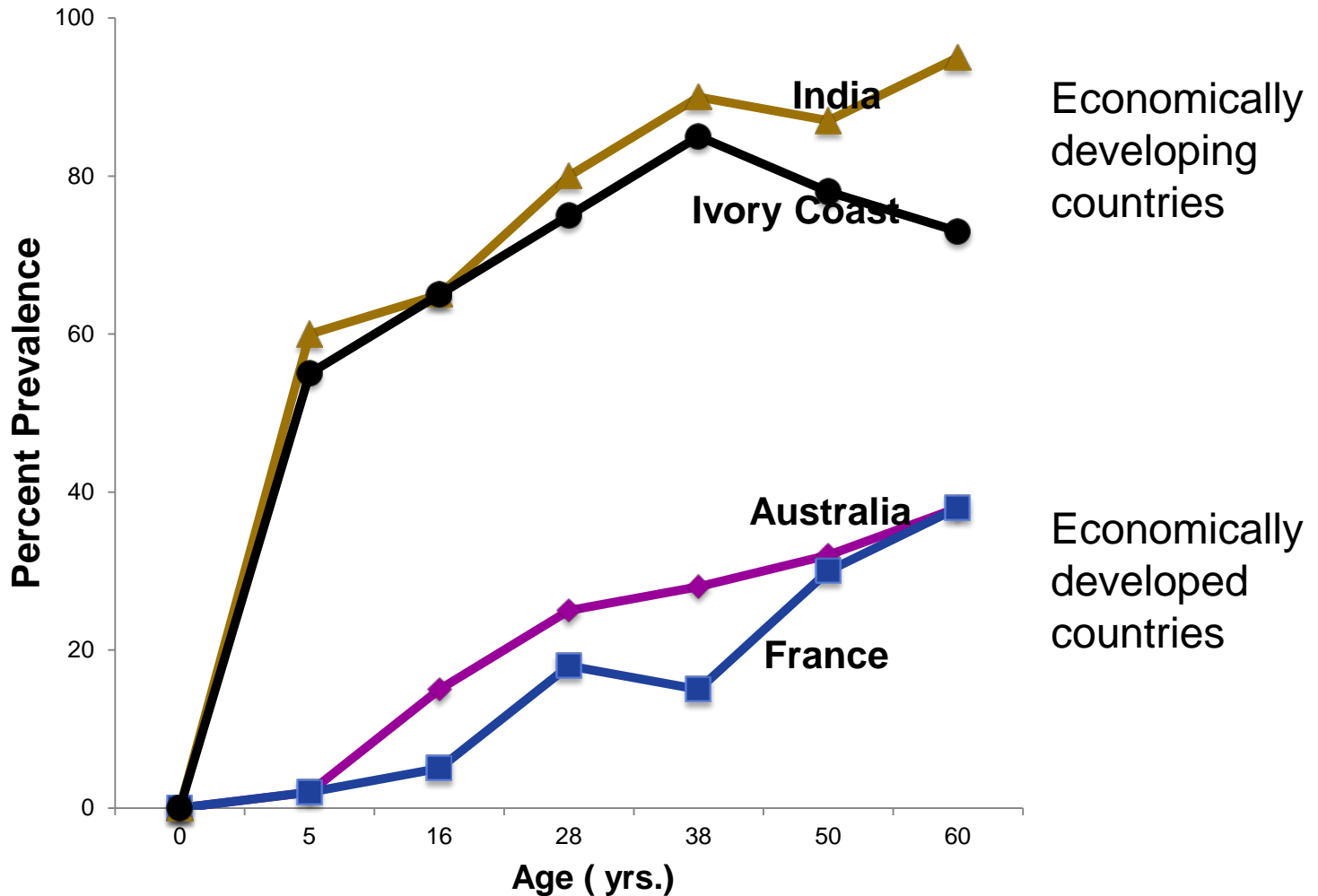
Routes of transmission

- Oral-oral
- Fecal-oral
- Possibly contaminated water



H. pylori prevalence increases with age

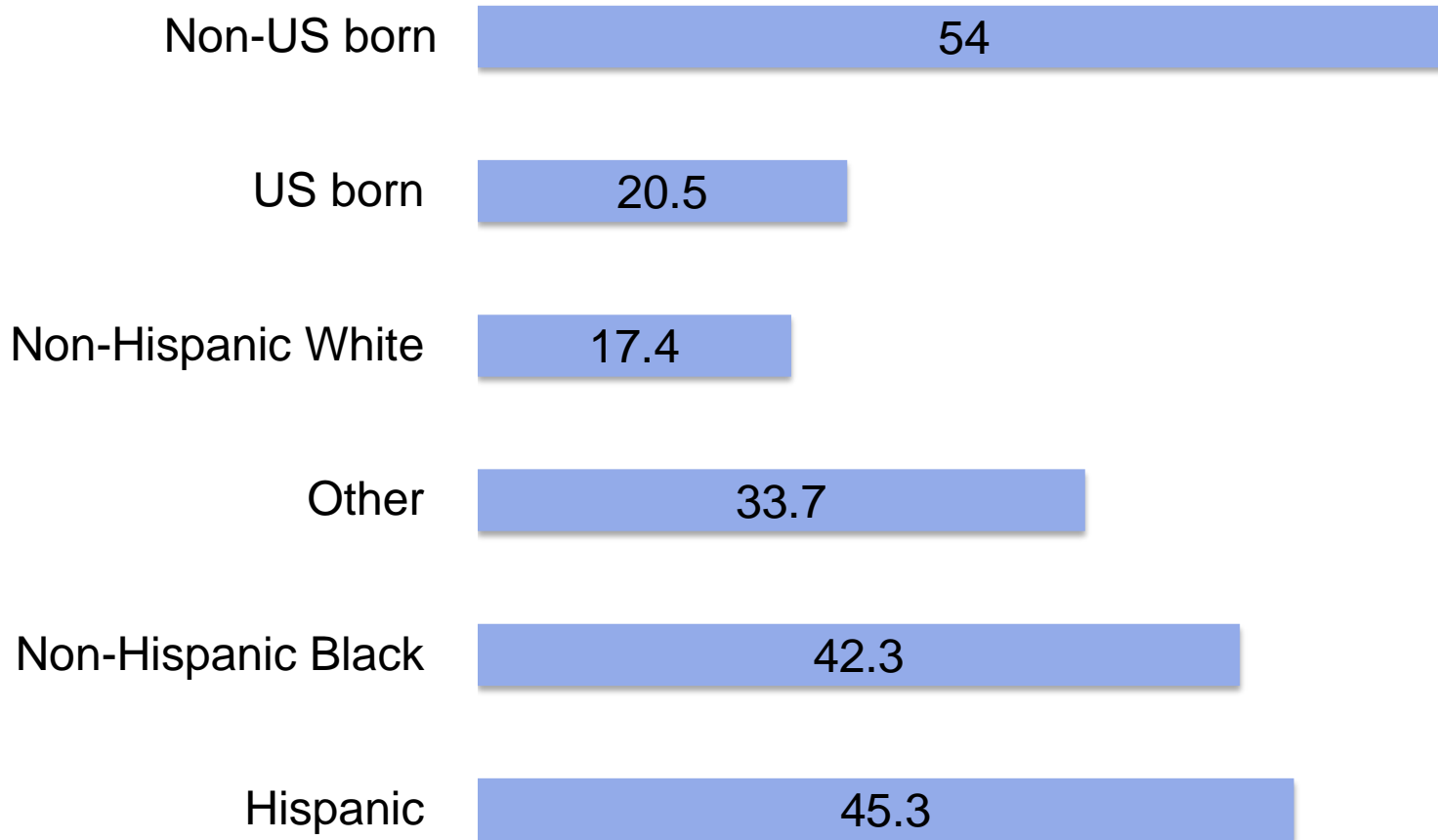
Infection pattern varies geographically and is related to economic status





H. pylori is a common infection

Disproportionally infects certain immigrant groups and minorities in the United States



Percent prevalence based on NHANES data



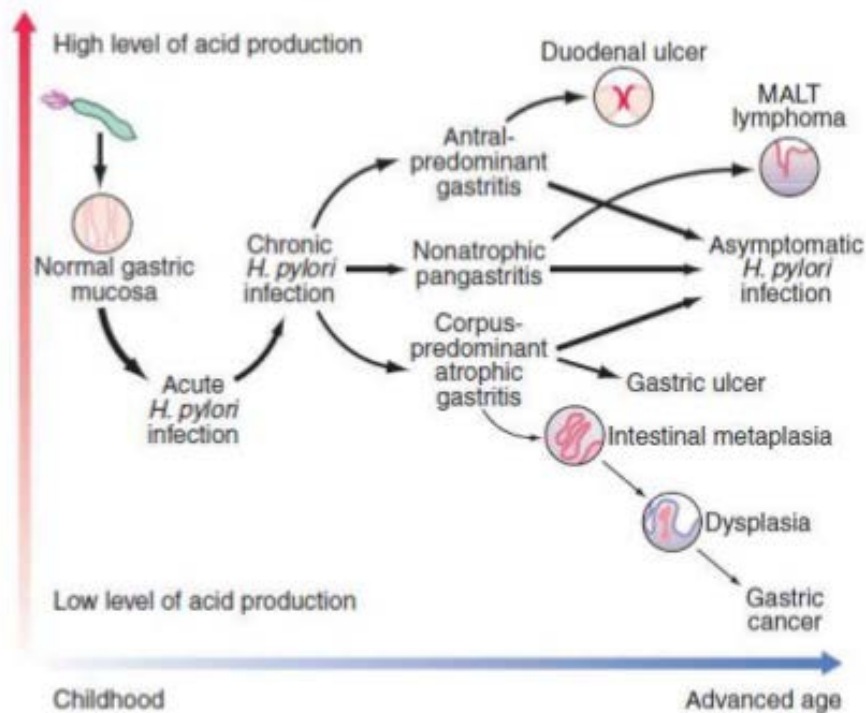
Concern for adverse health outcomes

IARC concluded that chronic infection with *H. pylori* is carcinogenic to humans

- *H. pylori* chronic infection increases the risk of non-cardia gastric cancer 3-fold
 - Based on evidence from over 16 nested case-control studies, a pooled analysis of >750 cases, 6 cohort studies, and 4 meta-analyses
- *H. pylori* chronic infection also increases risk of mucosa-associated lymphoid tissue (MALT) gastric lymphoma
 - Primarily based on studies showing that *H. pylori* treatment led to ~100% remission of cancer
- IARC also concluded there was sufficient evidence of the carcinogenicity of *H. pylori* from studies in experimental animals
 - Gastric cancer in *H. pylori*-infected gerbils and transgenic mice
 - MALT lymphoma in *H. pylori*-infected mice



Natural history of *H. pylori* infection



Chronic inflammation
Oxidative stress

Cellular proliferation
Altered gene expression,
Methylation and mutation

Longo DL et al. Harrison's gastroenterology & hepatology.
McGraw-Hill, New York, USA, 2010.



H. pylori contributes to 6.2% of all cancer

- *H. pylori* is a major risk factor for gastric cancer
 - Third leading cause of cancer mortality worldwide
 - US is a low-risk country for gastric cancer; however, cancer incidence and mortality shows racial disparity
 - Single agent is responsible for over 780,000 deaths from cancer
- Current question is not whether *H. pylori* causes cancer but how to prevent *H. pylori*-related cancer deaths



Strategies to prevent gastric studies

Focused on eradication of *H. pylori*

- *H. pylori* treatment typically involves combination of drugs; 1 to 3 antibiotics (such as clarithromycin, metronidazole, amoxicillin) often given with a proton pump inhibitor.
- Randomized trials estimated that *H. pylori* treatment reduces cancer risk by ~35%
- Screening and treatment programs have been shown to be cost-effective in both low-risk and high-risk countries
- Some concerns that screening could lead to increases in antimicrobial resistance and alter gut microflora
- Ongoing efforts to evaluate benefits of population screening programs
 - IARC working group report (2014) on *H. pylori* eradication as a strategy for preventing gastric cancer
 - Most countries do not have public health programs for gastric cancer prevention



Review of IARC monograph and literature searches

- U.S. exposure documented
- No new studies or information were identified that are not consistent with the IARC review
- Interest in cancer prevention was identified



Objective and approach

Strategy that takes advantage of IARC assessments

Cancer hazard
evaluation
component

Apply RoC listing criteria to IARC peer-reviewed assessments of cancer studies in humans and experimental animals for two cancer sites

Reach out to interagency partners

Substance
profile

Summarize key information of carcinogenicity using IARC monograph as a resource

Update US exposure information

Appendix

Summarize information on prevention strategies using IARC prevention working group report as a resource

Supplement with new studies or policies

Potentially reach out to subject matter experts



Rationale and public health significance

- Public health and environmental justice concerns
 - Major contributor to the global burden of cancer; especially for low-income countries
 - Concern for subpopulations in the US, especially minorities and certain immigrant groups
- Approach is to use IARC assessments and peer review of the scientific literature
- As per process, draft monograph will be peer reviewed by subject matter experts
- RoC review may help increase awareness of ongoing cancer prevention activities



Review questions and comments

1. Comment on the merit of the proposed project relative to the mission and goals of the NTP. The NTP's stated goals are to: *Provide information on potentially hazardous substances to all stakeholders; develop and validate improved testing methods; strengthen the science base in toxicology; coordinate toxicology testing programs across DHHS*
<http://ntp.niehs.nih.gov/go/about>.
2. Comment on the clarity and validity of the rationale for the proposed evaluation.
3. Comment on the strategy and approach proposed to meet the stated objectives of the evaluation. Are the objective and approach for the cancer evaluation reasonable and clearly articulated? Are you aware of other scientific issues that need to be considered?
4. Rate the overall significance and public health impact of this evaluation as low, moderate, or high.
5. Provide any other comments you feel NTP staff should consider in developing this evaluation.