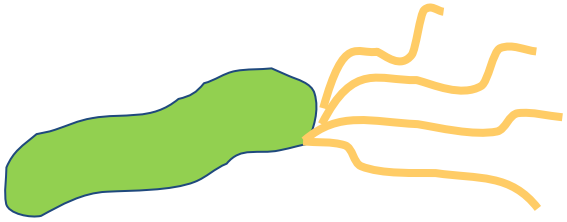
40 years of *Helicobacter pylori:* Chapter closed?



From proof of concept to clinical implementation

Peter Malfertheiner

LMU Universitätsklinik München
Med. Clinic II
München , Germany

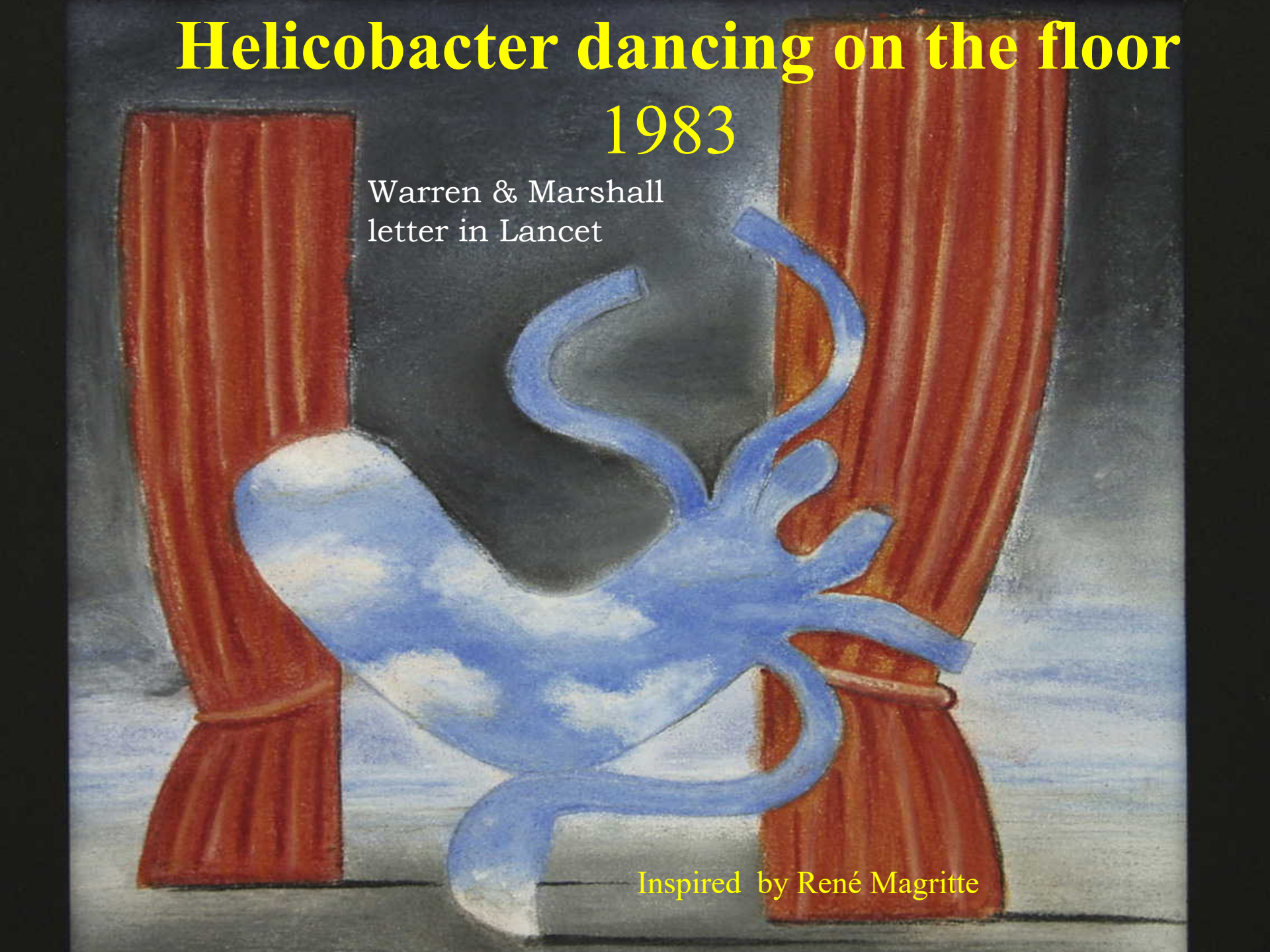
Prof Emeritus
Clinic of Gastroenterology, Hepatology
und Infectious diseases
Otto von Guericke Universität Magdeburg

European Helicobacter & Microbiota Study Group

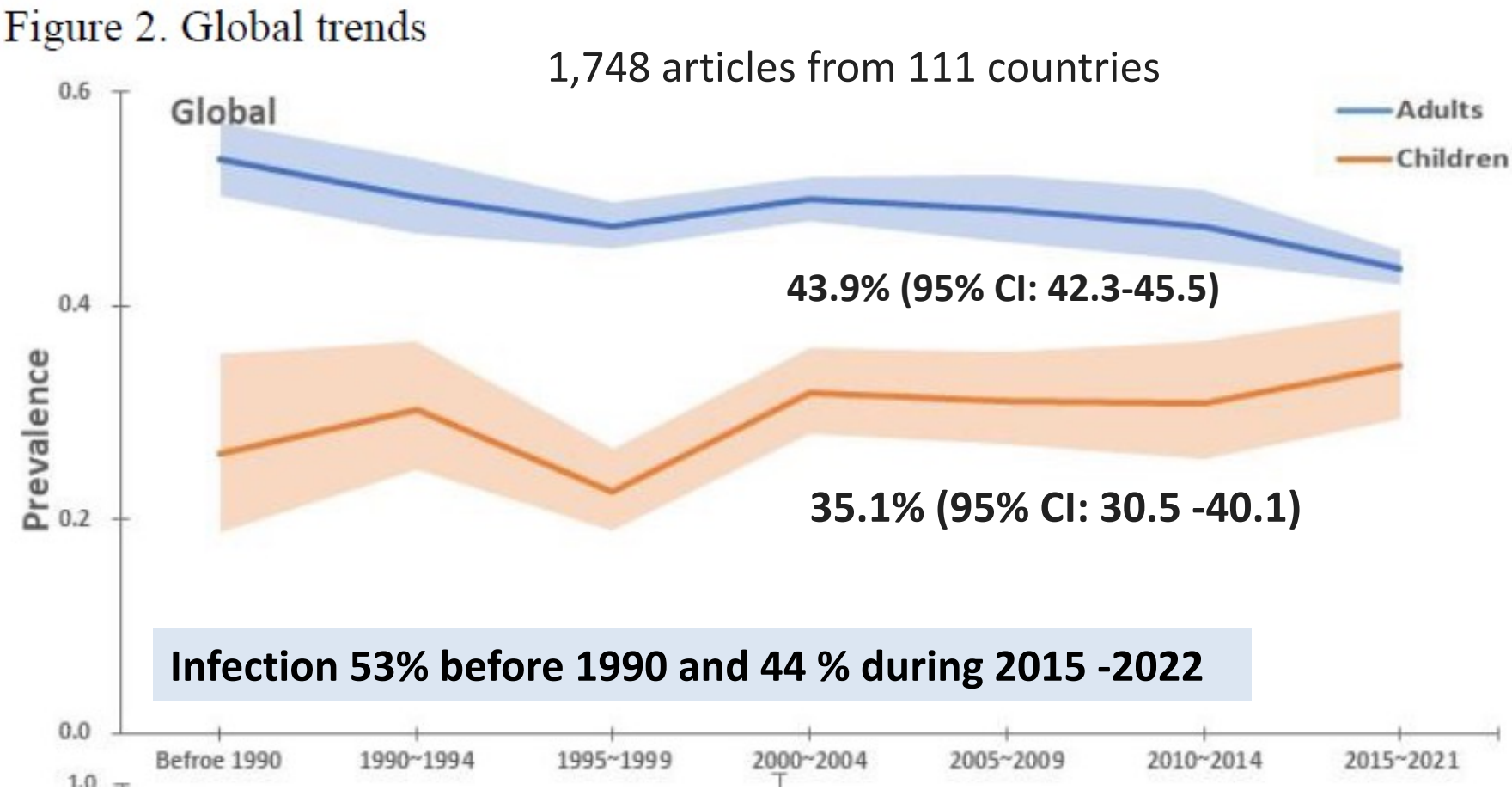
Conflicts of interest

- **Consultancies/speakers bureau:**

Aboca, Alfasigma,Allergosan,Bayer, Biocodex, Biohit,Cinclus, Malesci,Menarini,Richen,Phathom


Helicobacter dancing on the floor
1983
Warren & Marshall
letter in Lancet
Inspired by René Magritte

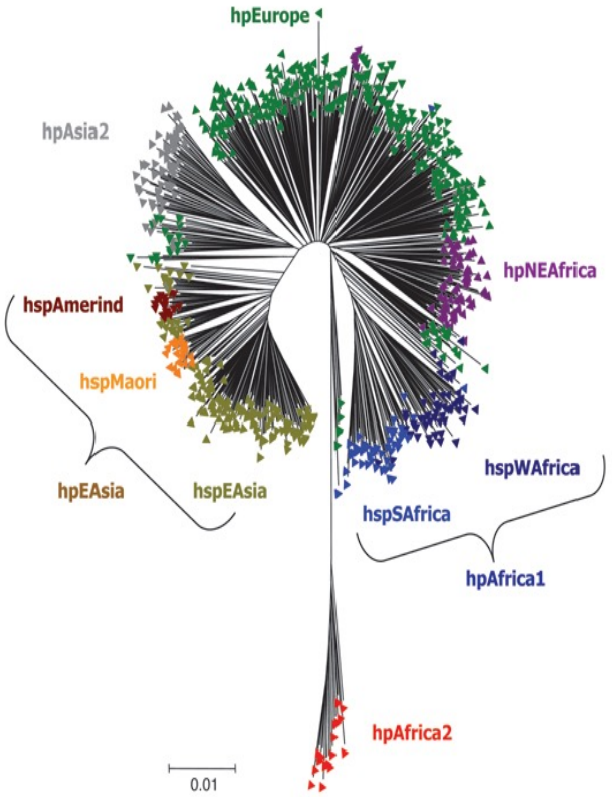
H.pylori prevalence in adults and children



Global prevalence of Helicobacter pylori infection and incidence of gastric cancer between 1980 and 2022.

Chen YC, Malfertheiner P, Yu HT, ..Liou JM. Gastroenterology. 2024 Apr;166(4):605-619.

H.pylori originates in Africa
Coadaptation with humans



- Humans have been colonized by *H.pylori* for about 60000 yrs
- *H.pylori* followed man during migrations giving rise to the present genotype distribution

Linz B et al, Nature 2007

DER ÖTZI The Iceman

H.pylori detected in the Iceman who lived 5300years ago

ANCIENT MICROBIOME

The 5300-year-old *Helicobacter pylori* genome of the Iceman

Frank Maixner,[1*†] Ben Krause-Kyora,[2†] Dmitrij Turaev,[3†] Alexander Herbig,[4,5†] Michael R. Hoopmann,[6] Janice L. Hallows,[6] Ulrike Kusebauch,[6] Eduard Egarter Vigl,[7] Peter Malfertheiner,[8] Francis Megraud,[9] Niall O'Sullivan,[1] Giovanna Cipollini,[1] Valentina Coia,[1] Marco Samadelli,[1] Lars Engstrand,[10] Bodo Linz,[11] Robert L. Moritz,[6] Rudolf Grimm,[12] Johannes Krause,[4,5‡] Almut Nebel,[2‡] Yoshan Moodley,[13,14‡] Thomas Rattei,[3‡] Albert Zink[1*‡]

The Iceman had a highly virulent strain,Cag A, Vac A s1 m1

inflammatory reaction in the stomach with high amounts of calprotectin

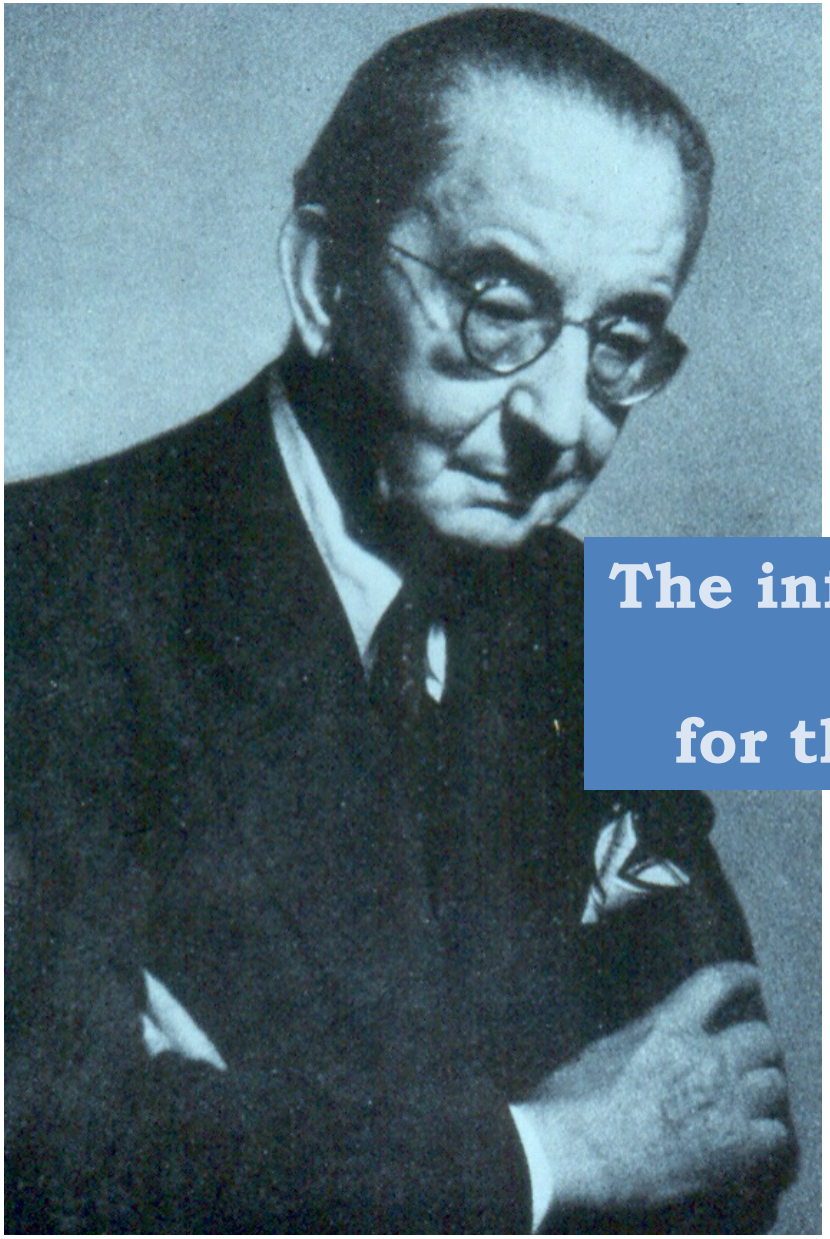
Science. 2016 Jan 8;351(6269):162-5

The history of Helicobacter pylori- 40 years of progress

Aim to attain to a chronological order

- **The discovery**
- **The first decade leads to the revolution in management of peptic ulcer disease**
- **Recognized as primary risk factor in gastric cancer**


….nothing more difficult to see than what is in front of your eyes!
J.W. Goethe



The inflamed gastric mucosa (Gastritis
essential condition
for the development of peptic ulcer

Theory rejected!!!!!

Konietzny 1926,surgeon

- ***A long history of gastric bacteria reported <u>before</u> the discovery of H.pylori***

- ***However causality in gastroduodenal pathologies was never proven***

<u>thus a role for bacteria in the stomach rejected</u>

American Medical Association

535 NORTH DEARBORN STREET • CHICAGO, ILLINOIS 60610

CABLE MEDIC, CHICAGO
TWX 312222-9032

AREA CODE 312
527-1500

THE JOURNAL OF THE
AMERICAN MEDICAL ASSOCIATION

JOHN H. TALBOTT, MD, *Editor*
ROBERT W. MAYO, *Executive Managing Editor*
LESTER S. KING, MD, *Senior Editor*

September 1, 1966

Paper rejected

Dr. J. Licudis
Patission 285
Athens, Greece

Dear Doctor Licudis:

Your manuscript, "Ulcer of the Stomach and Duodenum," has been reviewed by the editorial board. I regret that this does not seem quite appropriate for our journal, and we are unable to accept it for publication. I am returning the manuscript herewith. Tha for thinking of us.

Sincerely yours,

Lester S. King, M.D.

LSK:mu

Enc: MS #6446(C&pamphlet)

John Lykoudis

General practitioner in Greece

1958 first reported the antibiotic treatment of peptic ulcer disease

THE LANCET, JUNE 4, 1983

UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS

UNIDENTIFIED CURVED BACILLI ON GAS
EPITHELIUM IN ACTIVE CHRONIC GASTRITIS

SIR,—Gastric microbiology has been sadly neglected. Half the patients coming to gastroscopy and biopsy show bacterial colonisation of their stomachs, a colonisation remarkable for the constancy of both the bacteria involved and the associated histological changes. During the past three years I have observed small curved and S-shaped bacilli in 135 gastric biopsy specimens. The bacteria were closely associated with the surface epithelium, both within and between the gastric pits. Distribution was continuous, patchy, or focal. They were difficult to see with haematoxylin and eosin stain, but stained well by the Warthin-Starry silver method (figure).

I have classified gastric biopsy findings according to the type of inflammation, regardless of other features, as "no inflammation", "chronic gastritis" (CG), or "active chronic gastritis" (ACG). CG shows more small round cells than normal while ACG is characterised by an increase in polymorphonuclear neutrophil leucocytes, besides the features of CG. It was unusual to find no inflammation. CG usually showed superficial oedema of the mucosa. The leucocytes in ACG were usually focal and superficial, in and near the surface epithelium. In many cases they only infiltrated the necks of occasional gastric glands. The superficial epithelium was often irregular, with reduced mucinogenesis and a cobblestone surface.

When there was no inflammation bacteria were rare. Bacteria were often found in CG, but were rarely numerous. The curved bacilli were almost always present in ACG, often in large numbers and often growing between the cells of the surface epithelium (figure). The constant morphology of these bacteria and their intimate relationship with the mucosal architecture contrasted with the heterogeneous bacteria often seen in the surface debris. There was normally a layer of mucous secretion on the surface of the mucosa. When this layer was intact, the debris was spread over it, while the curved bacilli were on the epithelium beneath, closely spread over the surface (figure).

The curved bacilli and the associated histological changes may be present in any part of the stomach, but they were seen most consistently in the gastric antrum. Inflammation, with no bacteria, occurred in mucosa near focal lesions such as carcinoma or peptic ulcer. In such cases, the leucocytes were spread through the full thickness of the nearby mucosa, in contrast to the superficial infiltration associated with the bacteria. Both the bacteria and the typical histological changes were commonly found in mucosa unaffected by the focal lesion.

Curved bacilli on gastric epithelium.

Section is cut at acute angle to show bacteria on surface, forming network between epithelial cells. (Warthin-Starry silver stain; bar = 10 μm.)

Determinative Bacteriology. The stomach must not be viewed as a sterile organ with no permanent flora. Bacteria in numbers sufficient to see by light microscopy are closely associated with an active form of gastritis, a cause of considerable morbidity (dyspeptic disease). These organisms should be recognised and their significance investigated.

Department of Pathology,
Royal Perth Hospital,
Perth, Western Australia 6001

J. ROBIN WARREN

THE LANCET, JUNE 4, 1983

been transferred to the family Spirillaceae genus *Campylobacter.*[8] Campylobacters however, have "a single polar flagellum at one or both ends of the cell" and the campylobacter flagellum is unsheathed.[9] Warren's bacteria may be of the genus *Spirillum.*

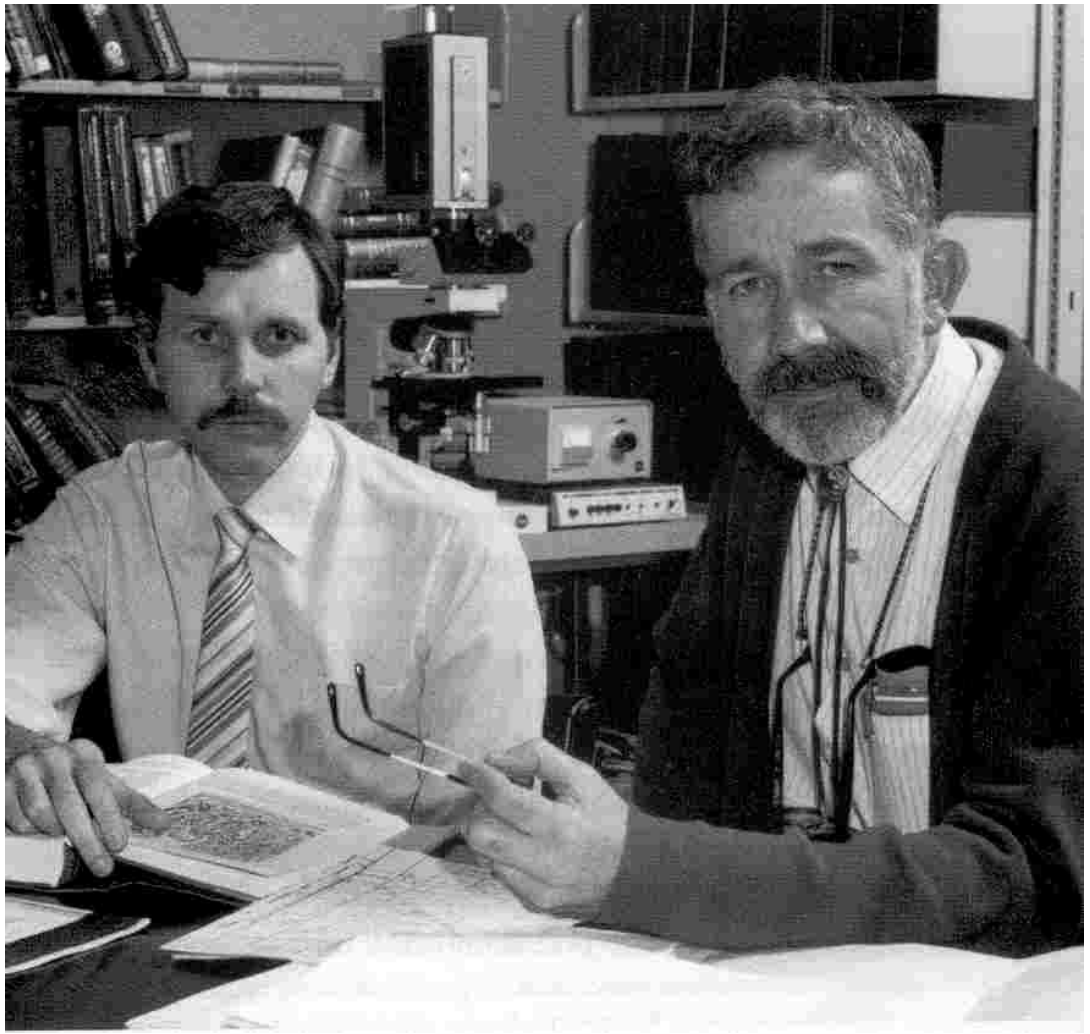
The pathogenicity of these bacteria remains unproven but their association with polymorphonuclear infiltration in the human antrum is highly suspicious. If these bacteria are truly associated with antral gastritis, as described by Warren, they may have a part to play in other poorly understood, gastritis associated diseases (ie, peptic ulcer and gastric cancer).

I thank Miss Helen Royce for microbiological assistance, Dr J. A. Armstrong for electronmicroscopy, and Dr Warren for permission to use fig 1.

Department of Gastroenterology,
Royal Perth Hospital,
Perth, Western Australia 6001

BARRY MARSHALL

If these bacteria are truly associated with antral gastritis…
they may have a part to play in other poorly understood gastritis associated diseases (ie peptic ulcer and gastric cancer)



Robin J Warren , the pathologist, the pioneer

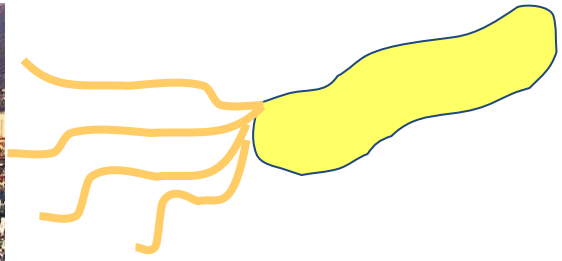
The long way from discovery to translate into clinical action

***H. pylori* gastritis an infectious disease**
-change in paradigme-

NEW in ICD 11

H.pylori gastritis is an infectious disease

asymptomatic/symptomatic w/wo complications



Maastricht V&VI –Florence consensus

Malfertheiner et al Gut 2017 & 2022

Kyoto consensus

Sugano et al 2015

Golden Pavilion, Kyoto

H.pylori gastritis presents with <u>structural and functional abnormalities</u>

All *H. pylori* infected patients require therapy

Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ.
Attempt to fulfil Koch's postulates for pyloric Campylobacter.
Med J Aust. 1985 Apr 15;142(8):436-9

A volunteer with histologically normal gastric mucosa received pyloric campylobacter by mouth. A mild illness developed, which lasted 14 days. Histologically proven gastritis was present on the tenth day after the ingestion of bacteria, but this had largely resolved by the fourteenth day

Barry´s H.p.self inoculation Fullfillment of Koch`s postulate, picture taken > 20 years later

SCANDINAVIAN JOURNAL OF Gastroenterology

Campylobacter pylori in Gastroduodenal Diseases: Current Views—Future Directions

Proceedings of an International Workshop
Copenhagen, 15 and 16 October 1987

Edited by

S. Gustavsson and P. Malfertheiner

Volume 23, Supplement 142, 1988

SJGSB8 23 (142) 1–116 (1988) ISSN 0085–5928

NORWEGIAN UNIVERSITY PRESS

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EUROPEAN CAMPYLOBACTER PYLORI STUDY GROUP

Provisional Steering Committee:

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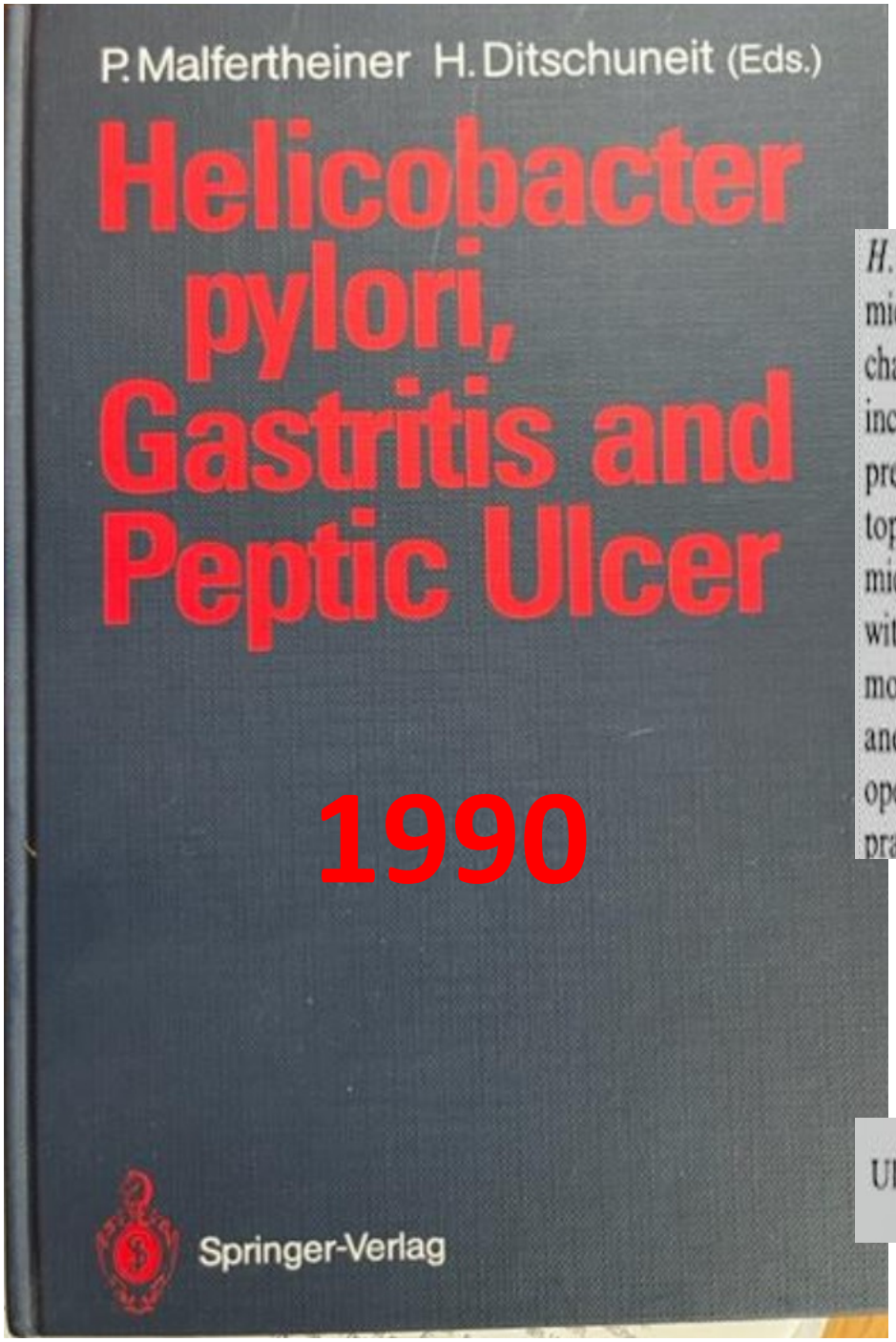
Peter Malfertheiner, FRG
Sven Gustavsson, Sweden
A. Gangl, Austria
A. M. Hirschl, Austria
José Pajares, Spain
Francis Mégraud, France

At the Campylobacter pylori meeting in Copenhagen, October 15–16, 1987 a "European Campylobacter Pylori Study Group" (ECPSG) was formed. The

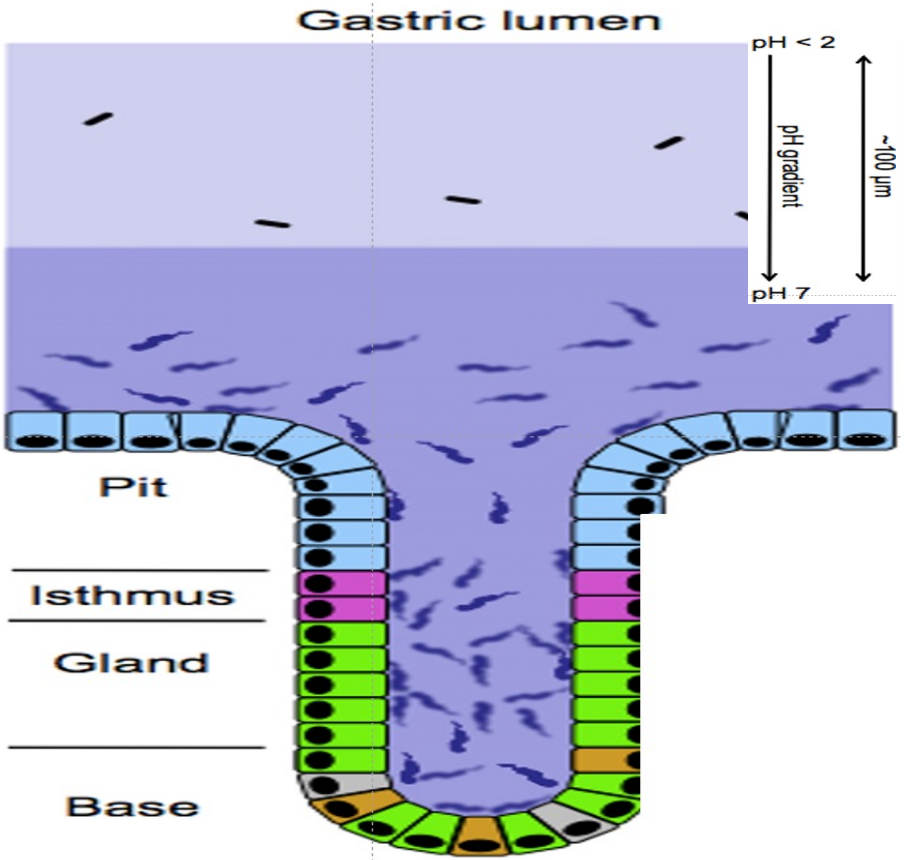
Transfer of Campylobacter pylori and Campylobacter mustelae to Helicobacter gen. nov. and Helicobacter pylon' comb. nov. and Helicobacter mustelae comb. nov., respectively

Goodwin CS et al Int] Syst Bacteriol 1989; 39: 397-405.



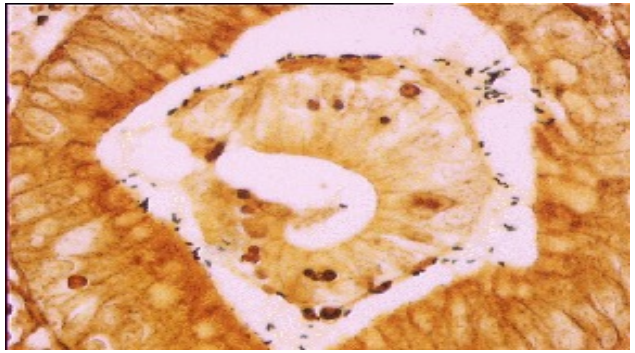
H. pylori has "scientifically infected" the whole world. Our understanding of the microbiological and pathogenetic aspects of *H. pylori* is continuously being challenged as new results follow swiftly from different research areas. This book includes an update and progress report on the various aspects of *H. pylori* presented and discussed in special workshops held during the meeting in Ulm. The topics covered in the book, written by leading scientists in this field, include microbiological features of *H. pylori*, its pathogenic mechanisms, interactions with the immune system, the response of the gastroduodenal mucosa to infection, morphological patterns of gastritis, the role of *H. pylori* in peptic ulcer disease, and attempts at curative treatment. Active researchers in this field and clinicians operating in the area of gastroduodenal diseases should find this book a source of practical and stimulating information.

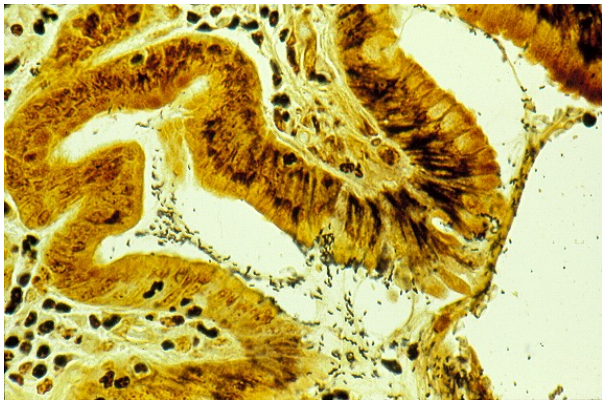
Ulm, 15th March 1990 PETER MALFERTHEINER · HANS DITSCHUNEIT

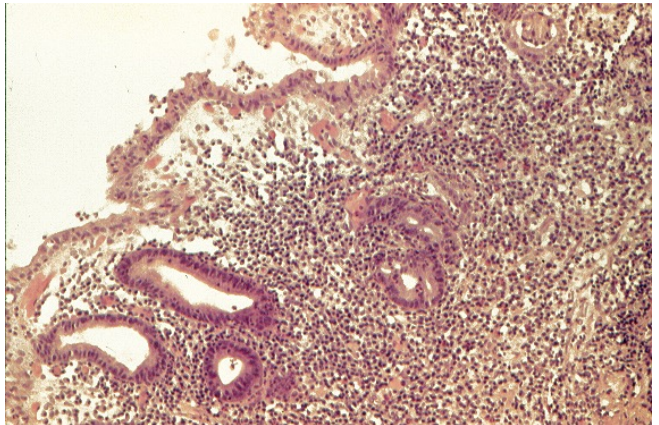


adapted from I.Yang et al Microbiol Rev 37 (2013) 736

H.pylori mucosal colonisation

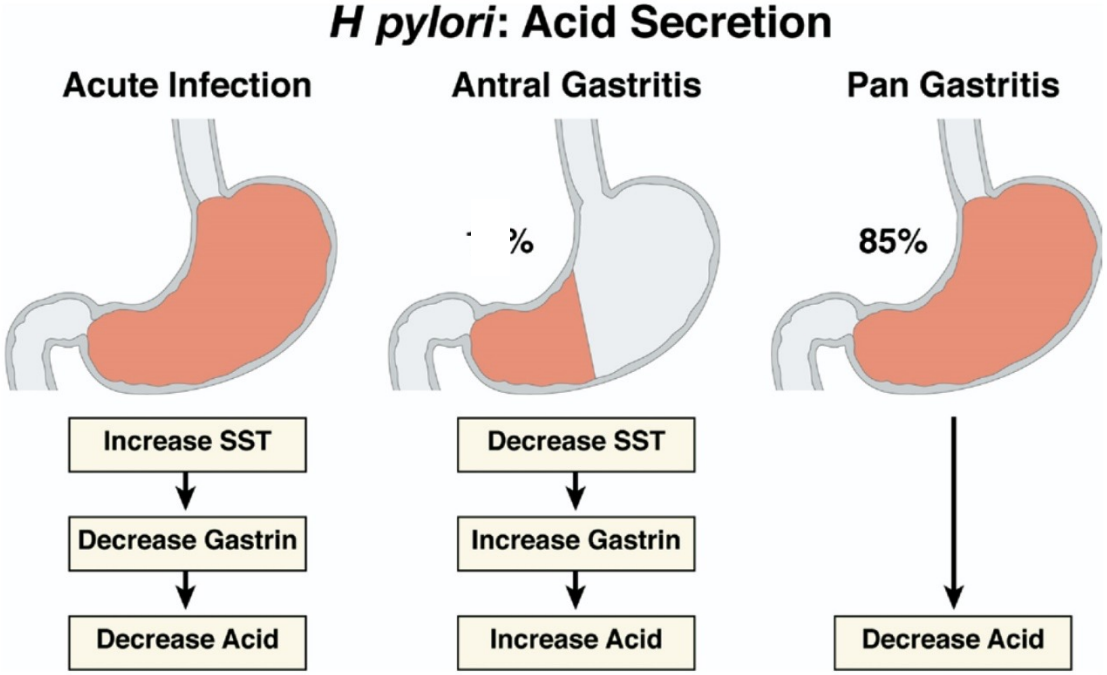






Chronic Gastritis

PEPTIC ULCER: GASTRIC ACID AND *H. pylori* INFECTION



- **Increased basal and stimulated acid production**
- Acid control central to the management
- Hp infection / pentagastrin PAO: ↑

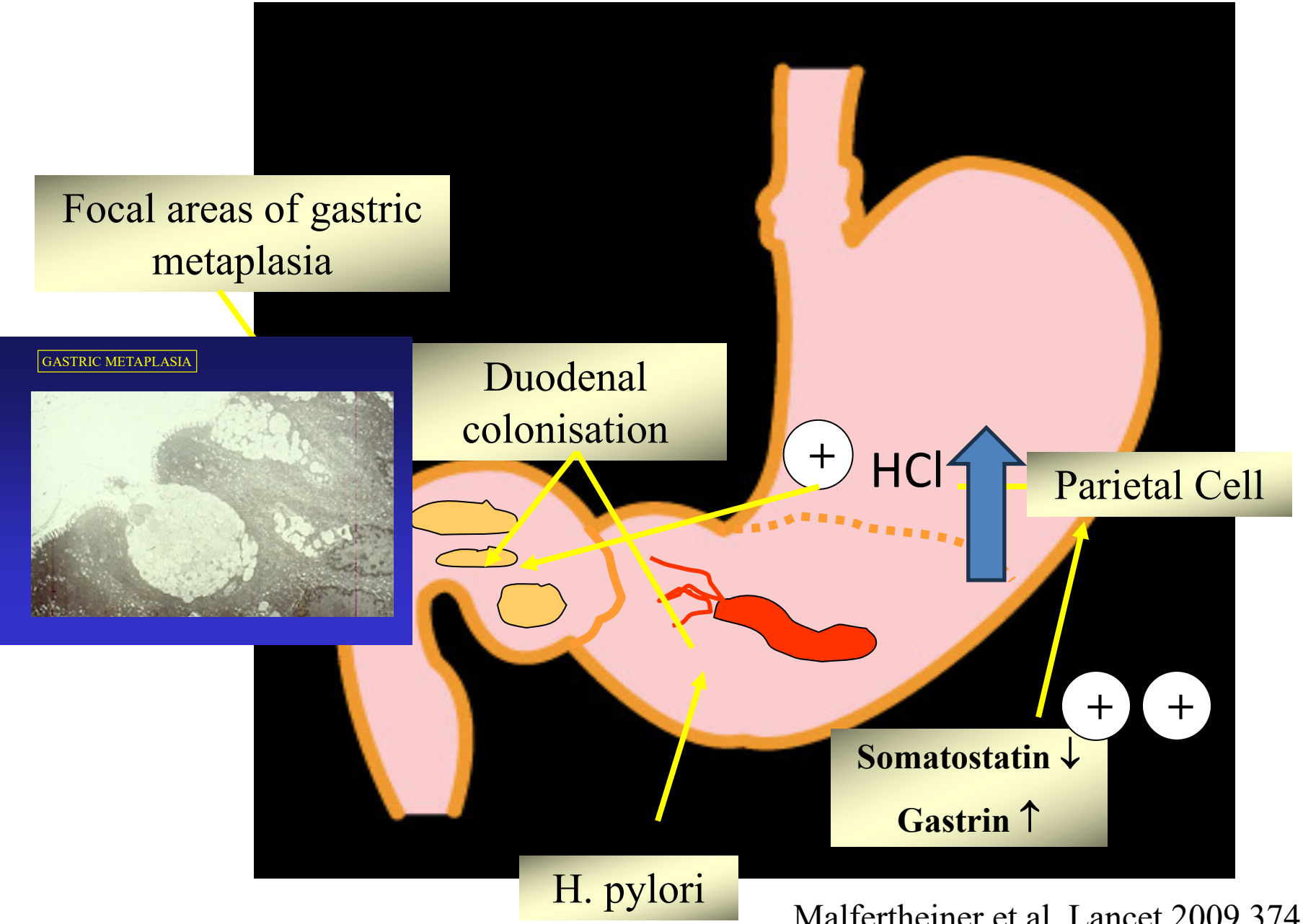
El-Omar EM et al. Gastroenterology 1995; 109:681-91.

Johnson HD and al. Gut 1964;5:402-11.

Duthie HL et al. Br J Surg 1977=;57:784-7

Howden CW, Hunt RH. Aliment Pharmacol Ther 1990;4:25-33

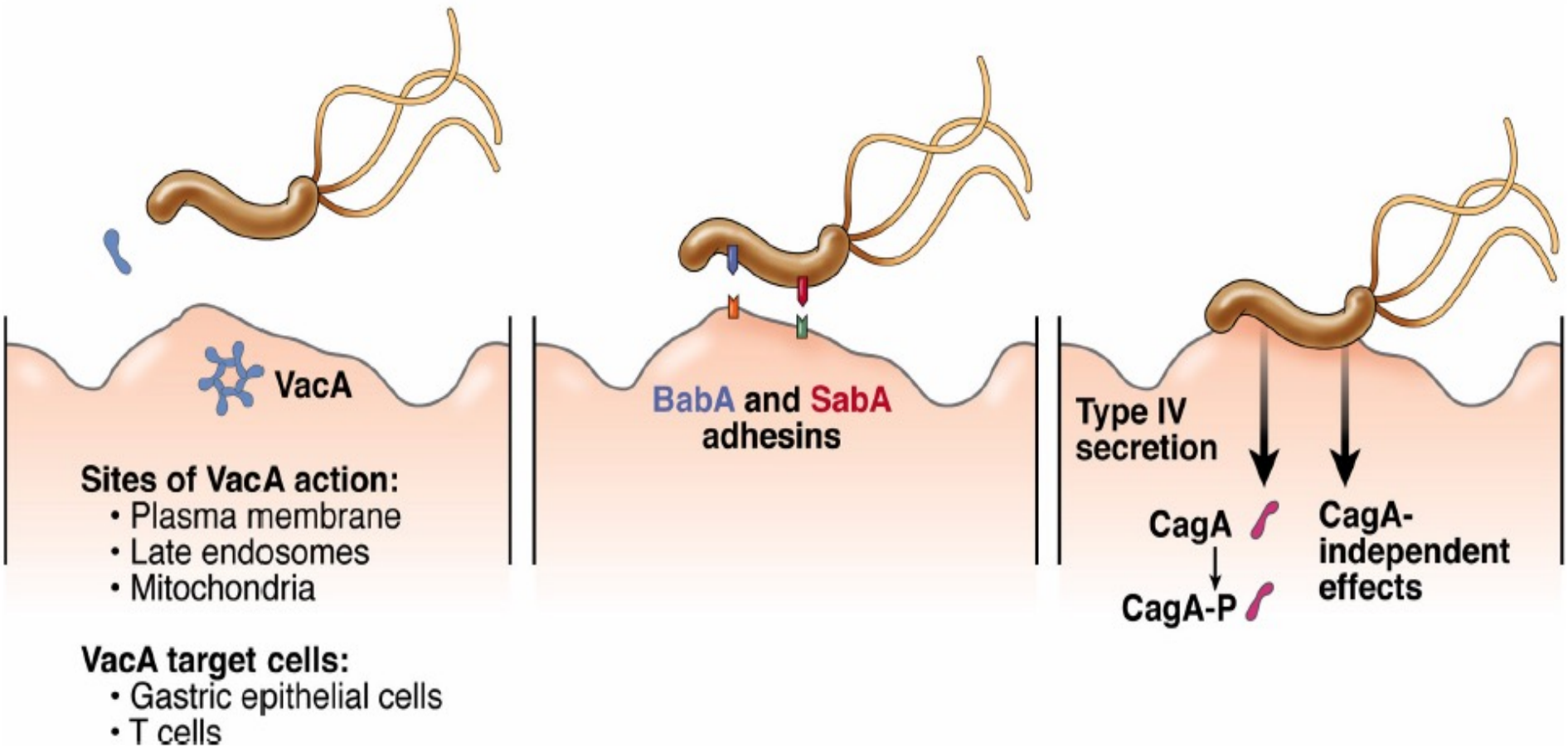
Duodenal Ulcer Pathophysiology in Antrum predominant Gastritis



Malfertheiner et al,.Lancet 2009,374,1449

Virulence factors and Interactions of H. pylori with human gastric mucosa

Basic science takes !



Cover TL, Blaser MJ. Purification and characterization of the vacuolating toxin from Helicobacter pylori.
J Biol Chem. 1992 May 25;267(15):10570-5.

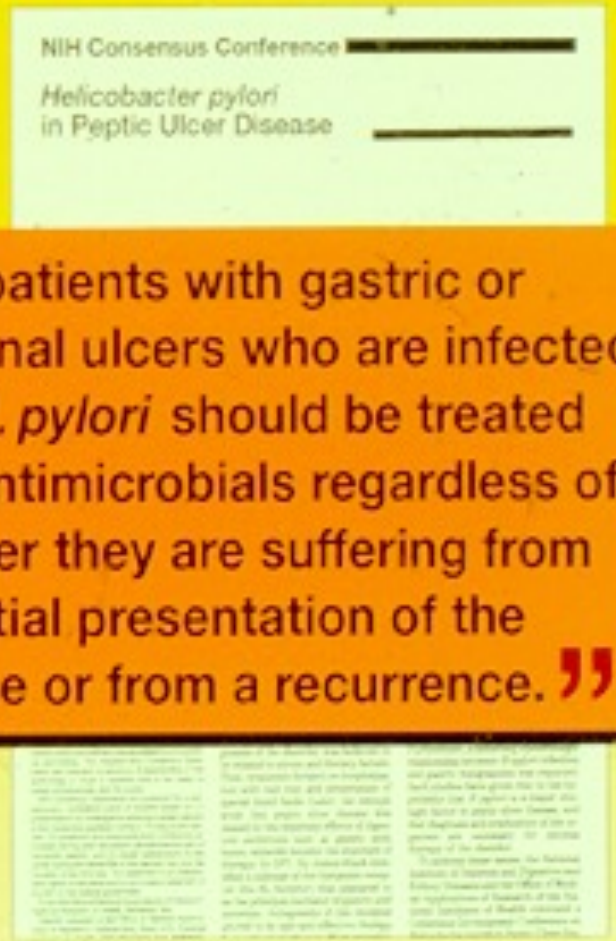
Cover and Blaser, Gastroenterology. 2009 May;136(6):1863-73

Peptic ulcer healing The revolutionary concept of roof repair

Peptic ulcer first indication for H.pylori eradication NIH consensus 1994

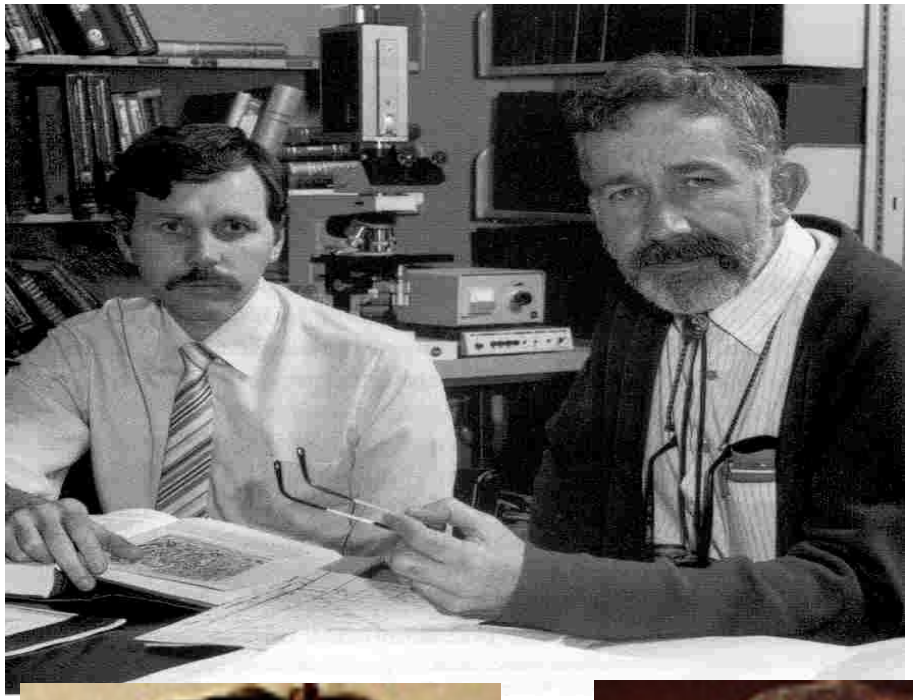
Helicobacter pylori in Peptic Ulcer Disease

1994


NIH Consensus Conference

Helicobacter pylori
in Peptic Ulcer Disease

"All patients with gastric or duodenal ulcers who are infected with *H. pylori* should be treated with antimicrobials regardless of whether they are suffering from the initial presentation of the disease or from a recurrence."



C.pylori(dis)- H.pylori

first cultured 1982

First published as letter 1983

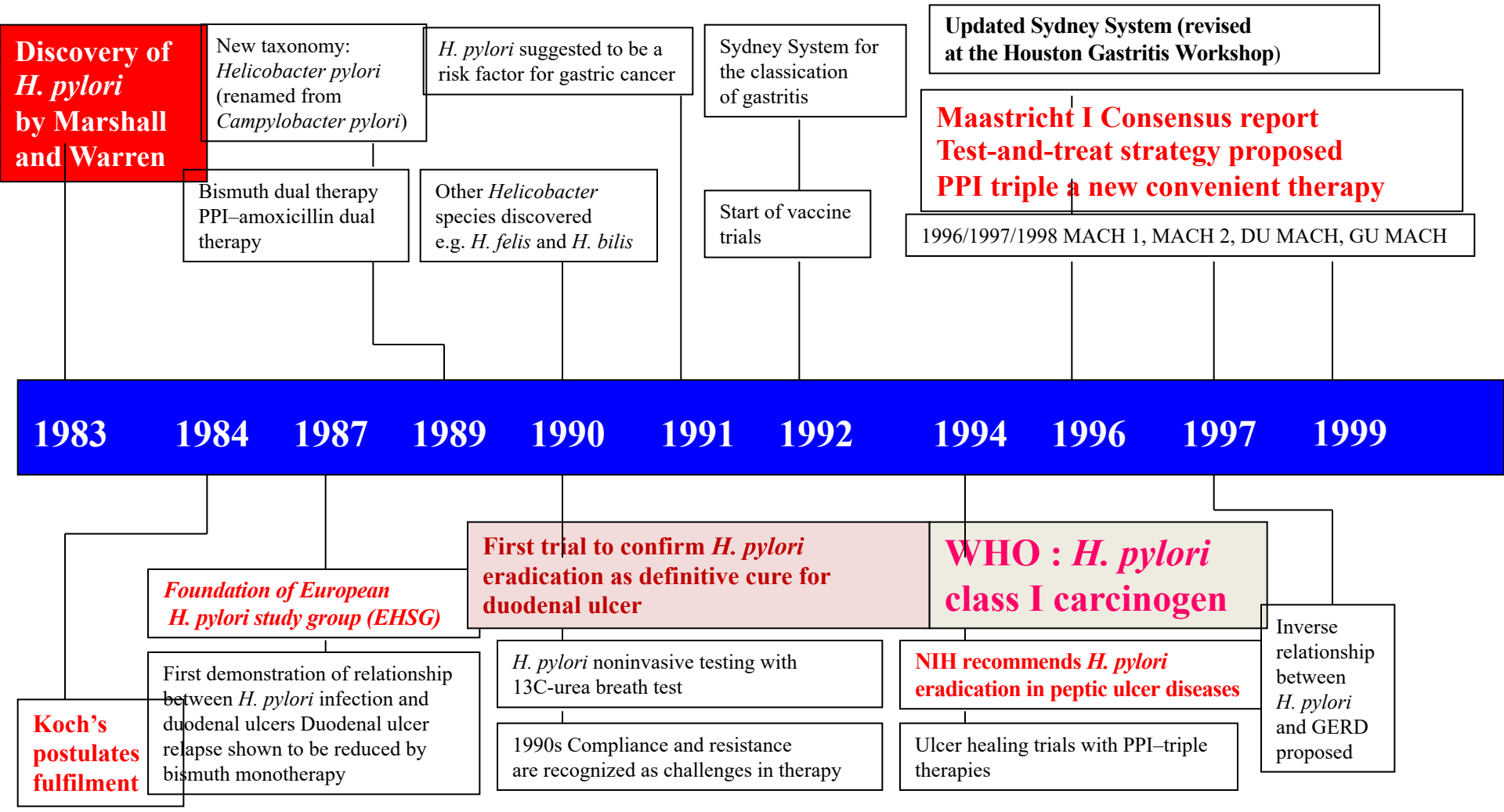
First full paper 1984

It took another 20 years

Nobelprice for medicine 2005

Timeline

Key developments in *Helicobacter pylori* clinical research



adapted from Malfertheiner P. et al. Nat. Rev. Gastroenterol. Hepatol. 2014, vol 11,no10,628-638

Evolution of ulcer therapy = H.pylori eradication

Post war → 1960s → 1970s → 1983 → 1990s → **1994**

H. pylori causes peptic ulcer change in paradigm

Diet
Antacids

Bismuth-compounds

S u r g e r y

H2 antagonists
± maintenance

PPI

mono-dual

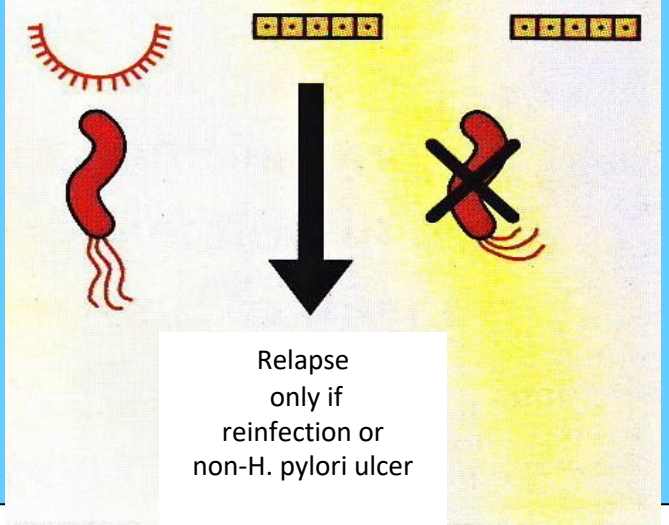
H. pylori

therapy

Combination of PPI with antibiotics

ulcer ⇒ healing ⇒ relapse

Ulcer ⇒ healing ⇒ cure



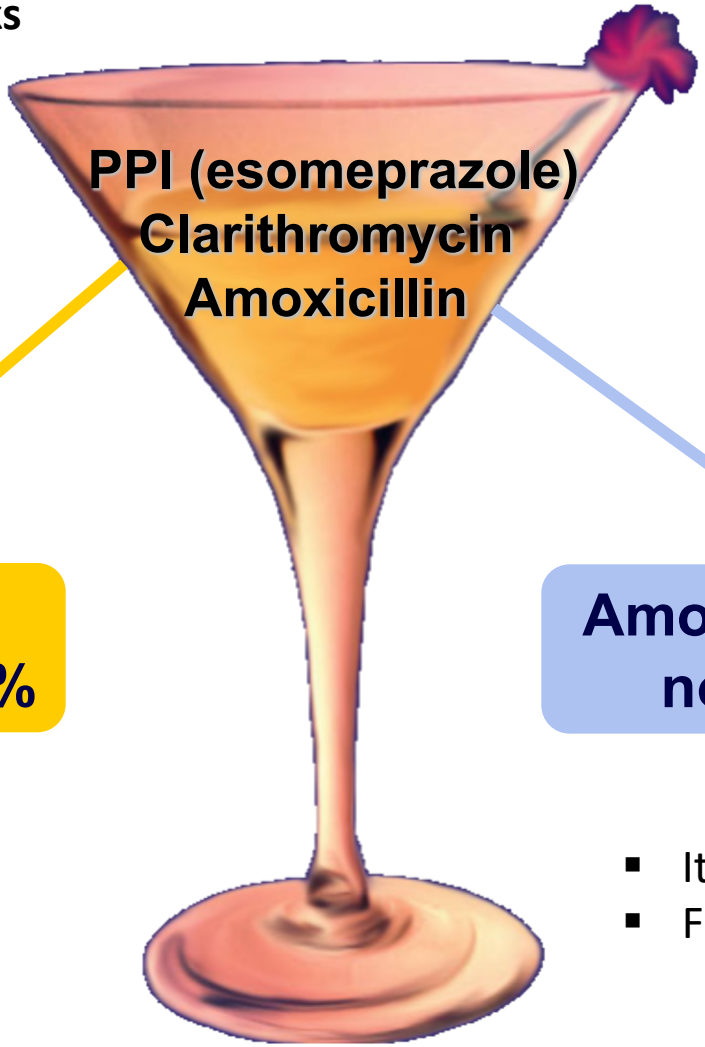
Relapse
only if
reinfection or
non-H. pylori ulcer

Short-term low dose triple therapy for the eradication of Helicobacter pylori

Bazzoli F, Zagari RM, Fossi S, Pozzato P, Alampi G, Simoni P, et al.
Eur J Gastroenterol Hepatol. 1994;6(9):773–8.

PPI Triple –the right fizz

H.pylori eradication in general 7 t0 14 days
In DU 7 to 14 days
In GU PPI additional 4 to 8 weeks



Clarithromycin if resistance <15 %

Metronidazole

or

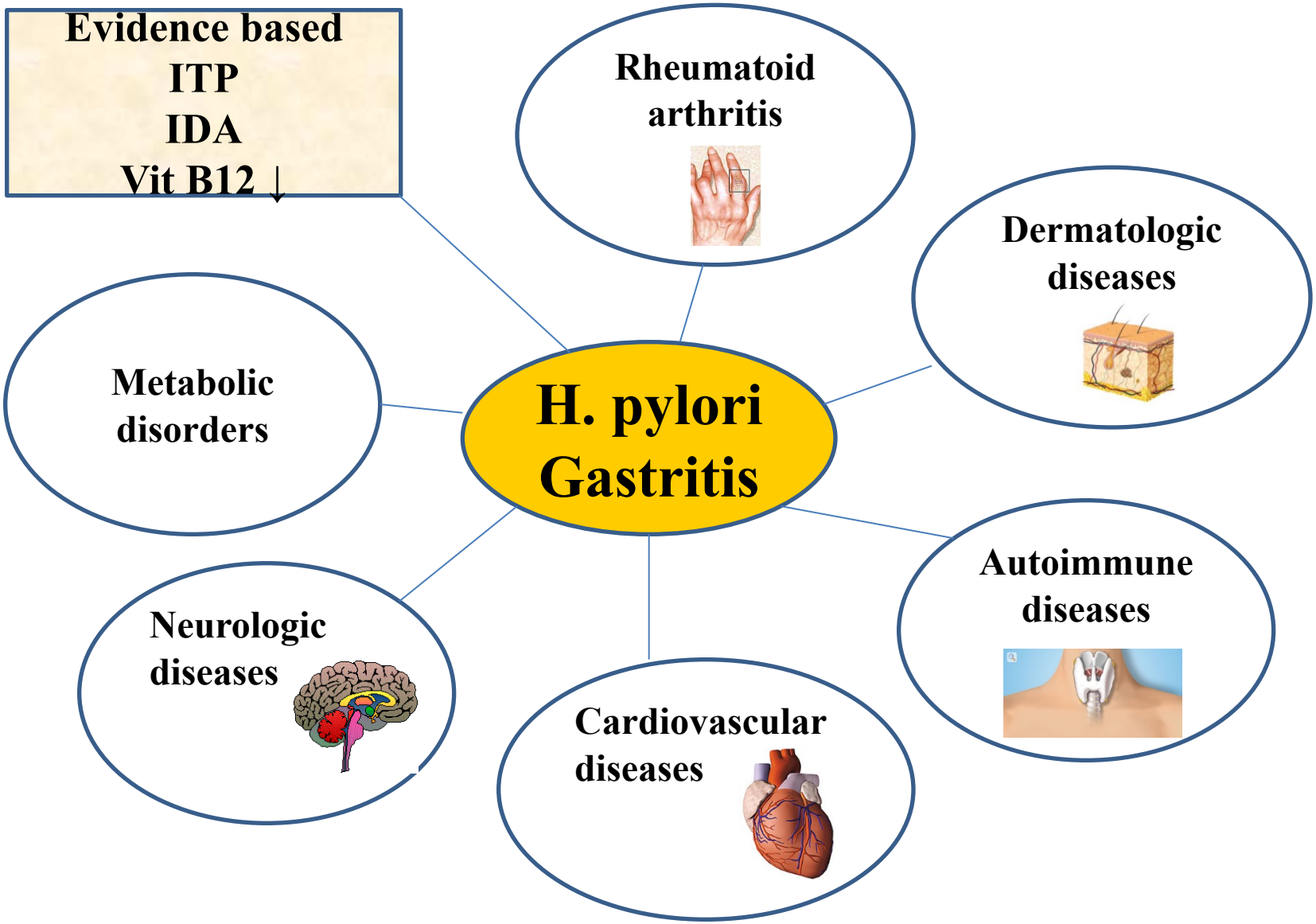
Amoxicillin almost no resistance

- Italian Triple Bazzoli
- French TripleLamouliatte

H.pylori and extragastric/ systemic diseases

Research started in mid 90`s

H. Pylori and extradigestive diseases



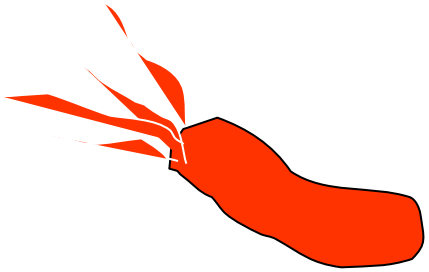
H.pylori and extragastric/ systemic diseases

First publications in late 90`s

Regression of Autoimmune Thrombocytopenia after Eradication of *Helicobacter pylori*.
Gasbarrini, A.; Franceschi, F.; Tartaglione, R.; Landolfi, R.; Pola, P.; Gasbarrini,G.*Lancet* **1998**, *352*, 878.

Clinical effects of Helicobacter pylori outside the stomach.
Franceschi F, Zuccalà G, Roccarina D, Gasbarrini A.
Nat Rev Gastroenterol Hepatol. 2014 Apr;11(4):234-42. doi: 10.1038/nrgastro.2013.243. Epub 2013 Dec 17. PMID: 24345888.

H. pylori: probiotic candidate!



Disease

Colonization

Intriguing relationship

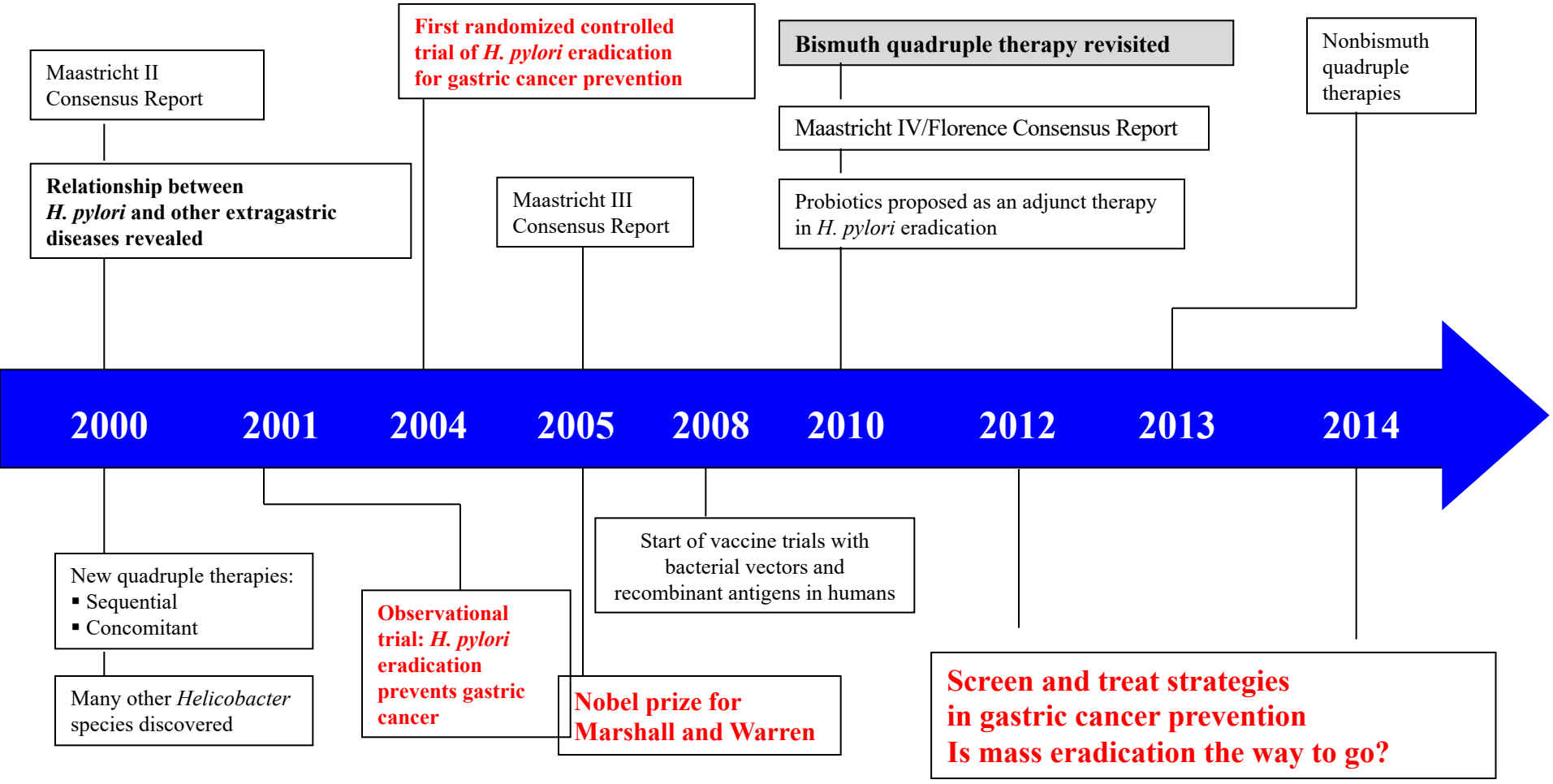
Host response

Protection from disease

Blaser, APT 2002

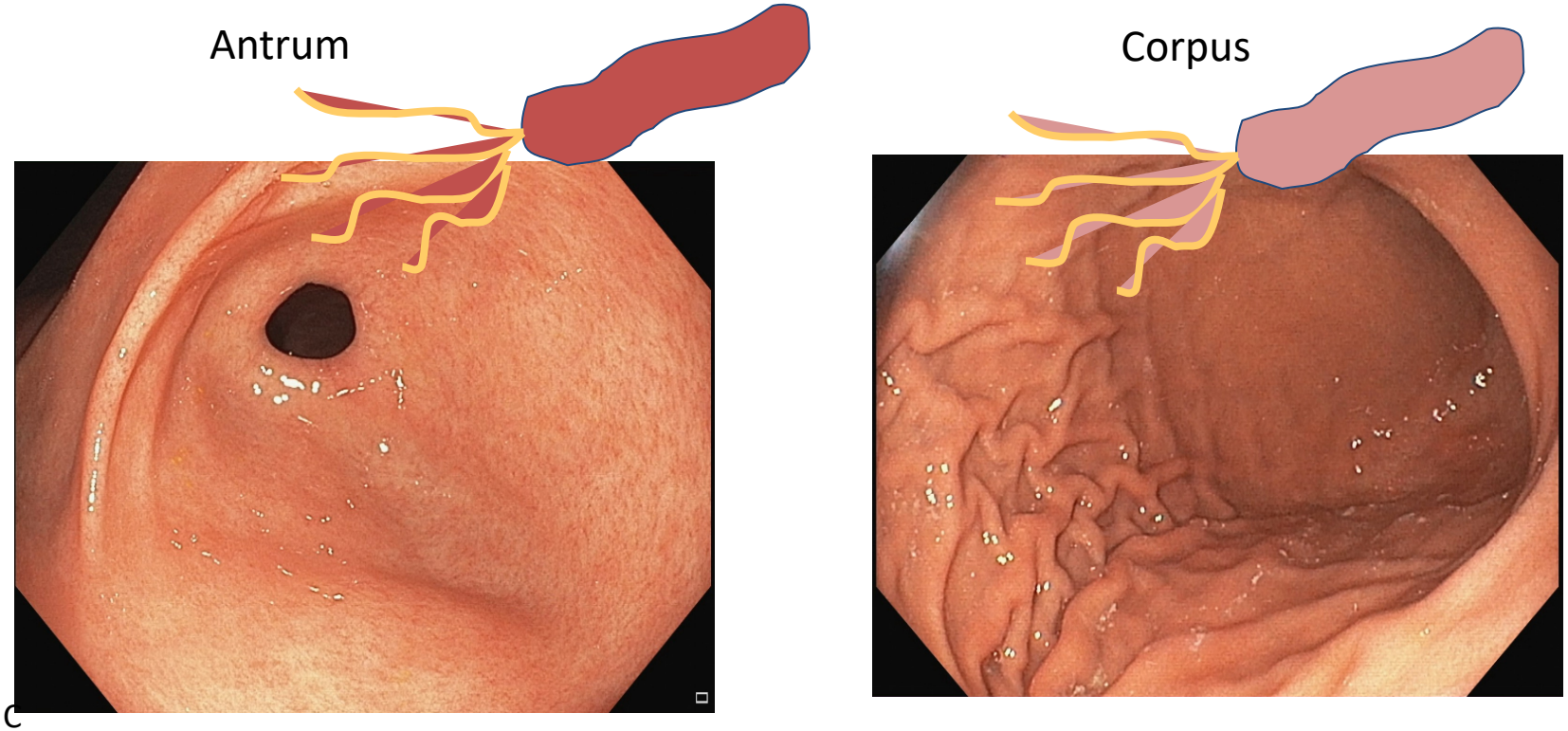
Key developments in *Helicobacter pylori* clinical research

Gastric Cancer prevention



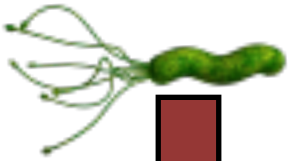
Malfertheiner, P. et al. Nat Rev Gastroenterol Hepatol. 2014 Oct;11(10):628-38

H.pylori Gastritis



❖ **H.pylori colonizes and <u>infects the whole stomach</u> and induces invariably chronic active gastritis**

H. pylori gastritis and gastroduodenal pathology



phenotypes

Gastric cancer phenotype

Antrum predominant Gastritis

- rare intestinal Metaplasia

Corpus predominant Gastritis

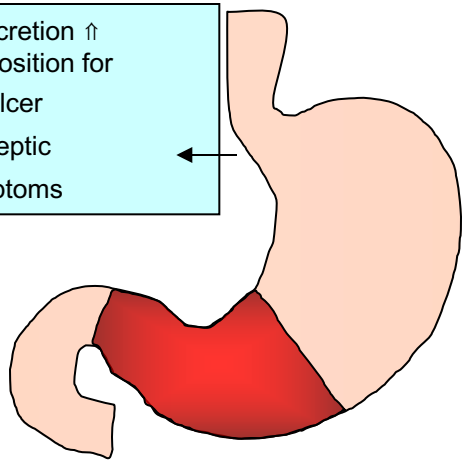
- Inflammation in the Corpus pronounced

Pangastritis,

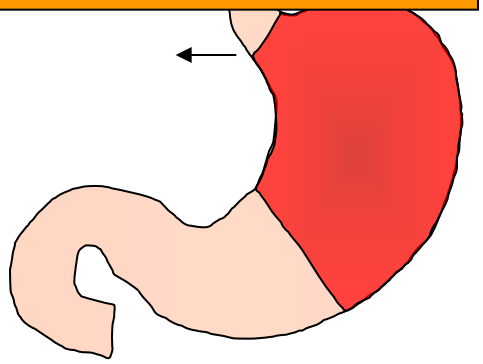
chronic atrophic /IM

- Atrophy severity variable

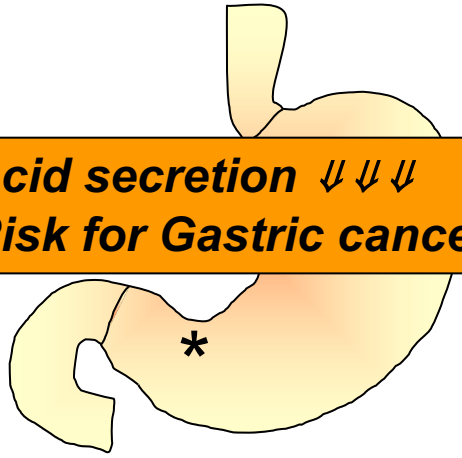
Acid secretion ⇑
Predisposition for
a) DU ulcer
b) dyspeptic Symptoms



Acid secretion ⇓ Predisposition for Gastric neoplasia/ Gastric ulcer

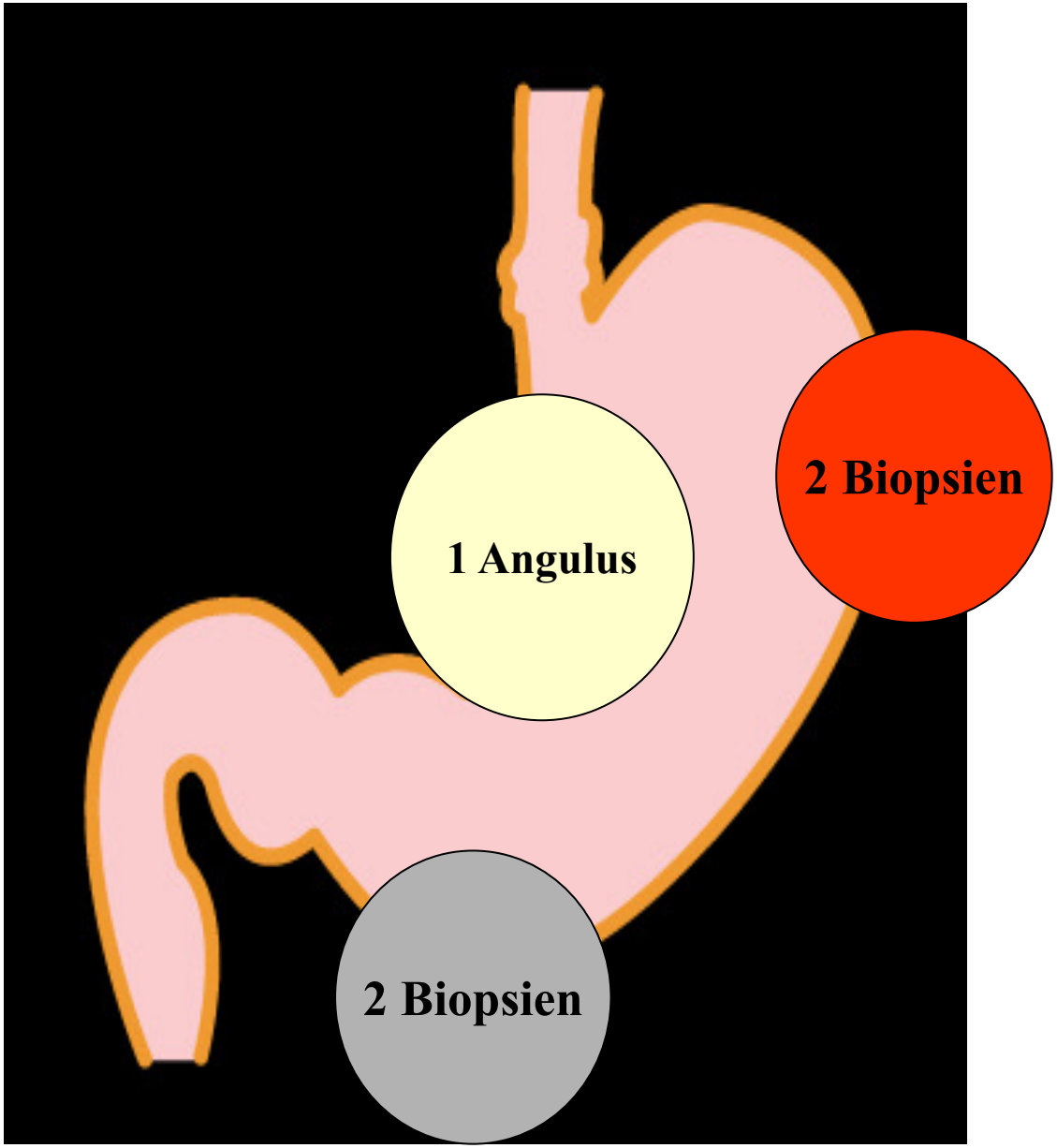


Acid secretion ⇓⇓⇓
Risk for Gastric cancer

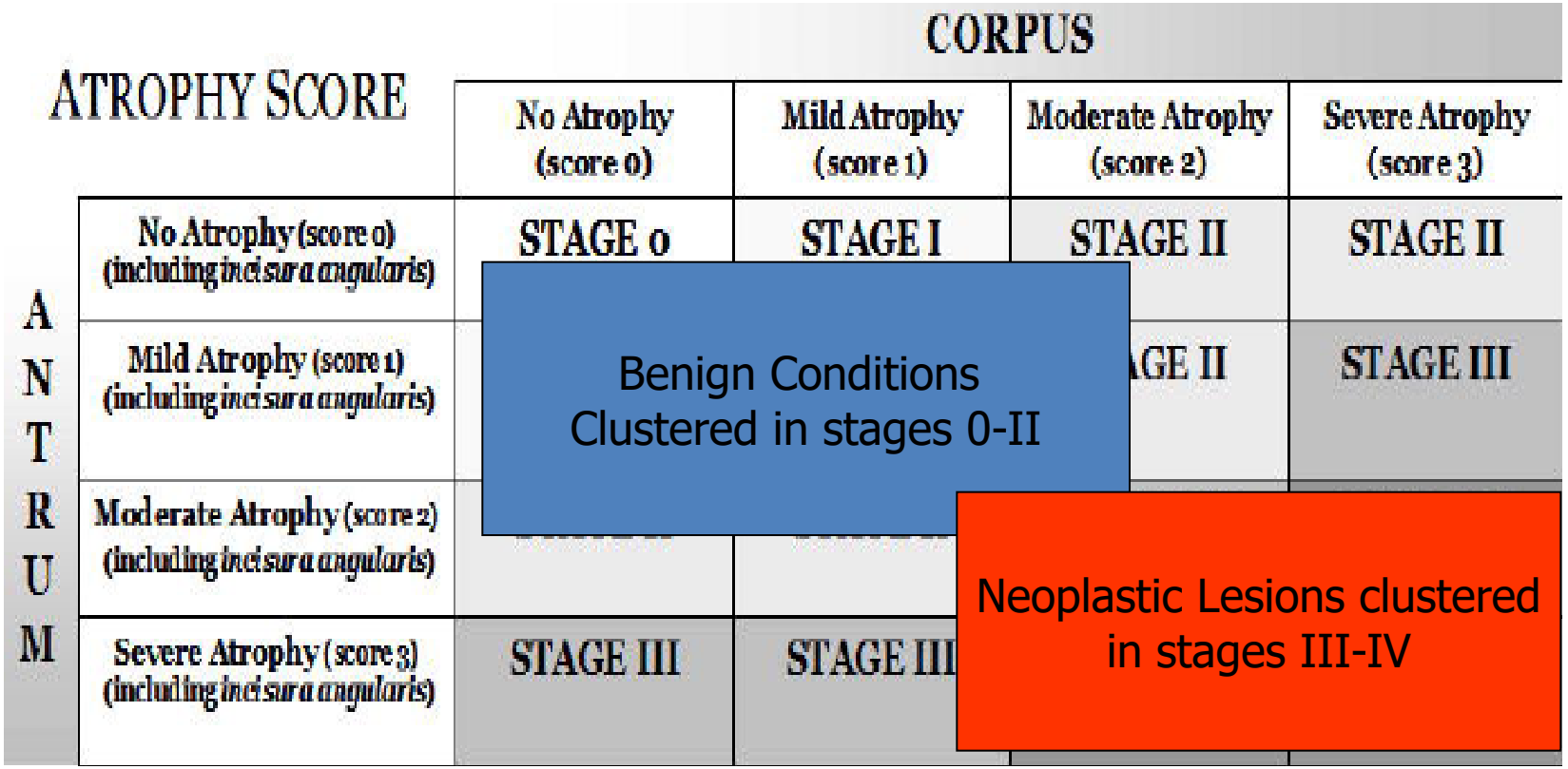


*with pronounced Atrophy +/- intestinal Metaplasia H. pylori can not persist

Histology based on the Sydney system 1991



Gastritis Grading: OLGA Staging



M. Rugge, Gastritis staging in clinical practice: the Olga staging system Gut. 2007

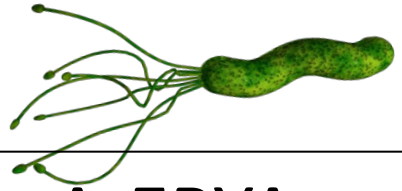
H. pylori and gastric cancer

The EVIDENCE

- Epidemiology
- bacterial virulence
- host susceptibility
- environmental factors
- histological cascade
- Molecular mechanisms
- Clinical observations ∞ clinical trial

H. pylori and gastric carcinogenesis

Bacterial virulence factors



Cag A-EPYA

Vac A-allelotypes

Host factors

Environmental

Tobacco

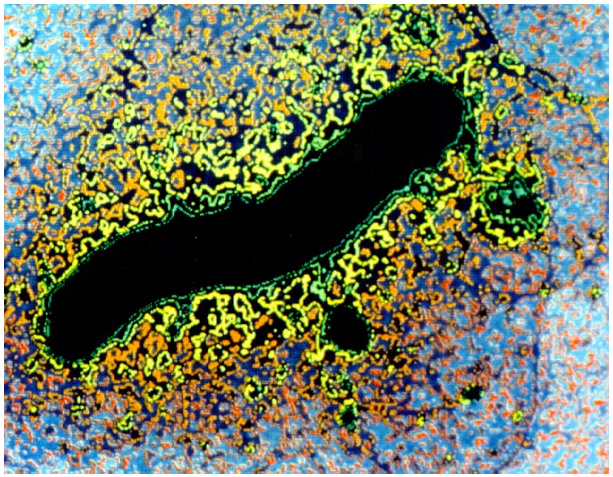
Diet

Polymorphisms of inflammatory cytokines

Gastric cancer–complex disease triggered by H.pylori

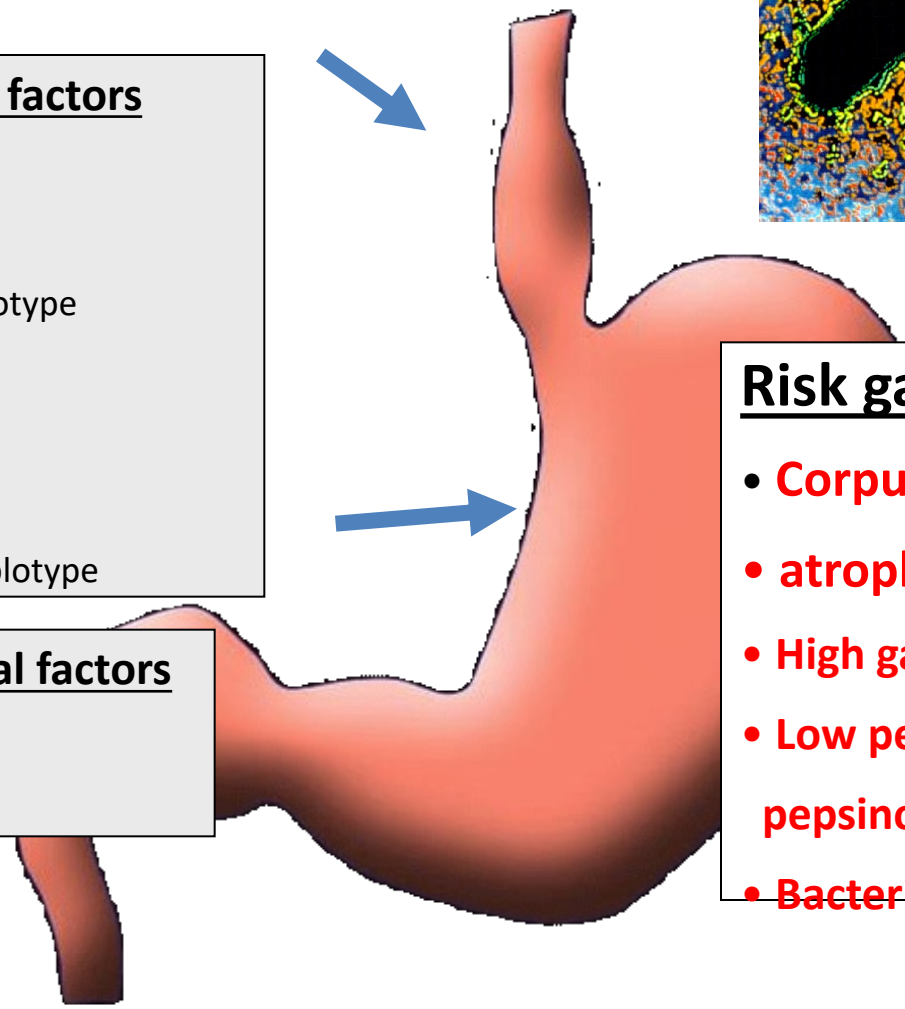
Bacterial virulence factors

- cagA PAI
- Vac A s1/m1



Host genetic factors

- IL-1B-511*T
- IL-1_RN*2*2
- IL-10 ATA haplotype
- TNF-A-308*A
- IL-8-251*A
- TLR4+896*G
- MBL2 HYD haplotype



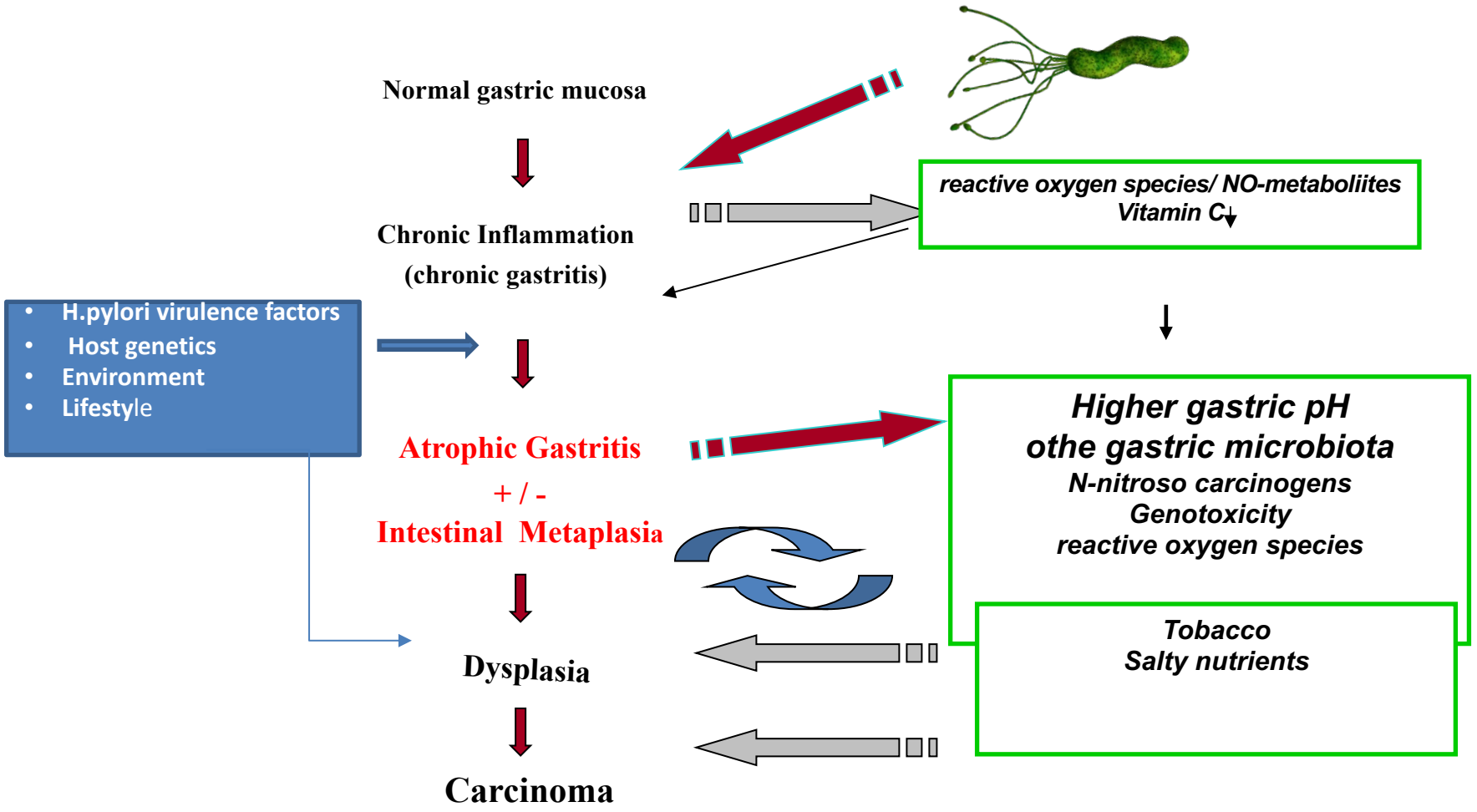
Environmental factors

- smoking
- **Dietary factors**

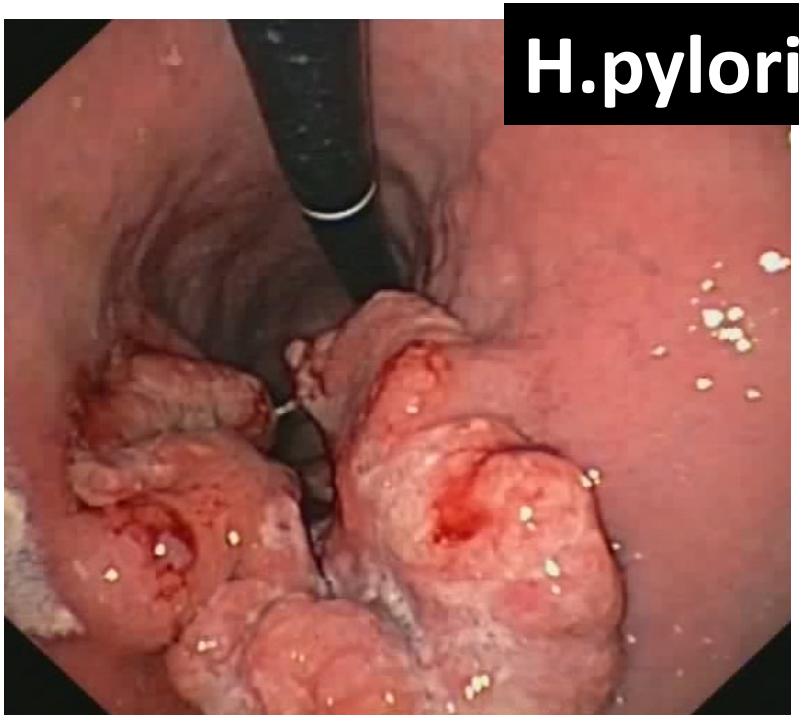
Risk gastritis

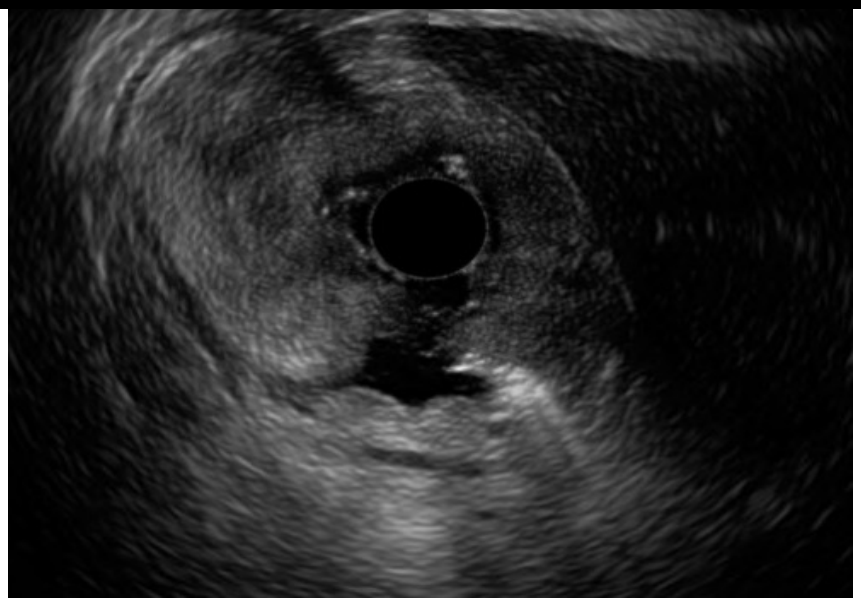
- **Corpus-predominant gastritis**
- **atrophic gastritis**
- **High gastrin + Hypochlorhydria**
- **Low pepsinogen I and pepsinogen I/II ratio**
- **Bacterial overgrowth**

H.pylori Gastritis and the „Correa“ cascade towards gastric cancer



H.pylori and gastric cancer





Statement 1:

H pylori infection is the **most consistent risk factor** for gastric cancer. Its elimination is therefore the **most promising strategy to reduce the incidence of gastric cancer.**

Evidence Level: 1a **Grade of Recommendation: A**

H pylori infection is associated with a 6-fold increased risk of gastric cancer.

- A prospective cohort study showed that gastric cancer developed in 2.9% of individuals infected with H pylori after 7.8 years

- did not develop in any of the individuals who were negative for H pylori

Helicobacter pylori infection and the development of gastric cancer
Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. N Engl J Med. 2001 Sep 13;345(11):784-9.

Gastric Cancer Study Group. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial.
Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS; China JAMA. 2004 Jan 14;291(2):187-94.

- **<u>Prospective, randomized, placebo-controlled,</u> population-based primary prevention study of 1630 healthy carriers of H pylori infection from Fujian Province, China,**

In the subgroup of H pylori carriers without precancerous lesions, eradication of H pylori significantly decreased the development of gastric cancer.

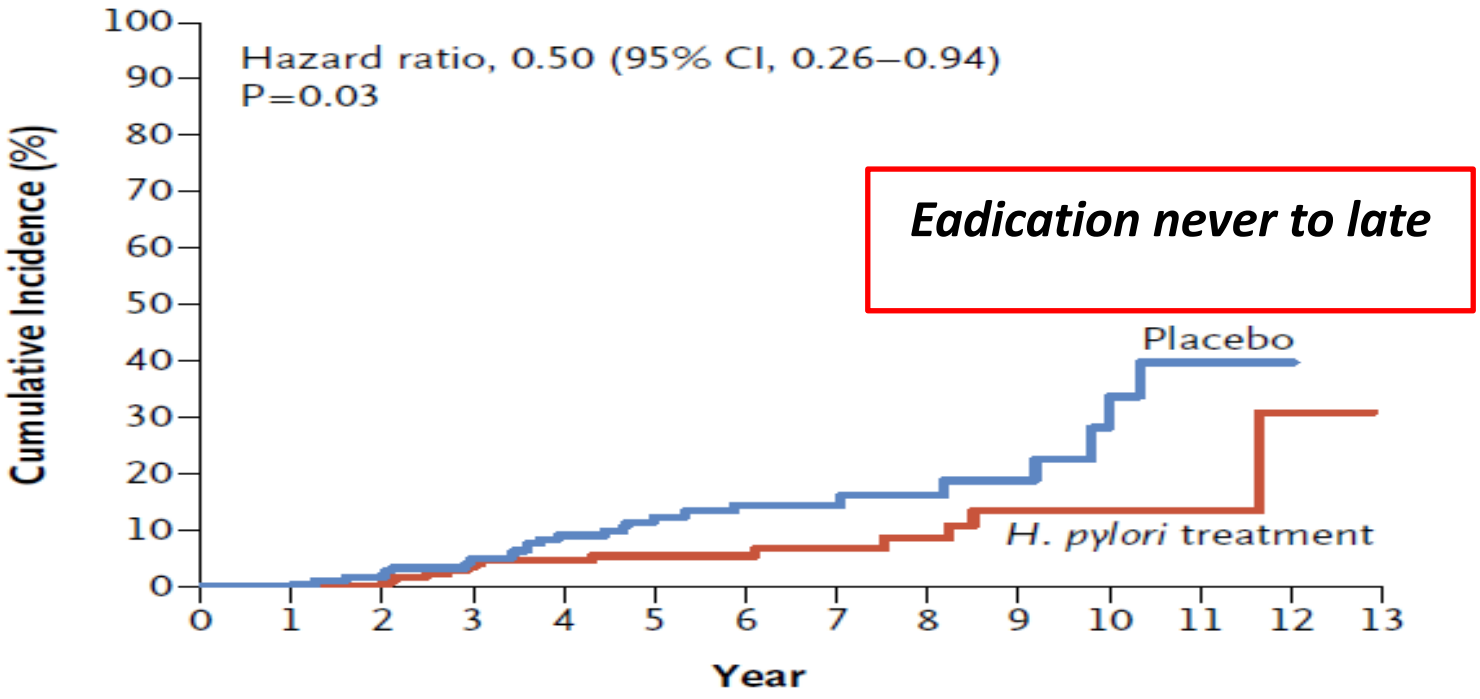
POINT of NO Return

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 22, 2018 VOL. 378 NO. 12

Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer

Il Ju Choi, M.D., Ph.D., Myeong-Cherl Kook, M.D., Ph.D., Young-Il Kim, M.D., Soo-Jeong Cho, M.D., Ph.D.,



Eadication never to late

No. at Risk

Placebo	202	188	175	158	125	95	67	51	34	25	12	6	1	0
H. pylori treatment	194	187	175	162	128	96	79	62	44	26	11	9	2	0

Endorsing Academies

Prof. Dr. Roberto J. J. Williams
President Academia Nacional de Ciencias Exactas, Físicas y Naturales Argentina

Prof. Dr. Andrew Holmes
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President Brazilian Academy of Sciences

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President Chinese Academy of Sciences

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President Académie des Sciences France

Prof. Dr. Jörg Hacker
President Nationale Akademie der Wissenschaften Leopoldina Germany

Prof. Dr. Ajay K. Sood
President Indian National Science Academy

Prof. Dr. Sangkot Marzuki
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President King Abdulaziz City for Science and Technology, Saudi Arabia

Prof. Dr. Jonathan Jansen
President Academy of Science of South Africa

Prof. Dr. Myung Chul Lee
President Korean Academy of Science and Technology South Korea

Prof. Dr. Ahmet Cevat Acar
President Turkish Academy of Sciences

Prof. Dr. Venkatraman Ramakrishnan
President Royal Society United Kingdom

G20 GERMANY 2017
SCIENCE 20 DIALOGUE

IMPROVING GLOBAL HEALTH

STRATEGIES AND TOOLS TO COMBAT COMMUNICABLE AND NON-COMMUNICABLE DISEASES

Executive Summary

Communicable (infectious) and non-communicable (non-infectious) diseases seriously endanger individual wellbeing and global health, and threaten the global economy. Strong short- and long-term evidence-based strategies are needed. The G20 Academies of Sciences call for (1) the strengthening of healthcare and public health systems, (2) applying existing and emerging knowledge, (3) addressing the

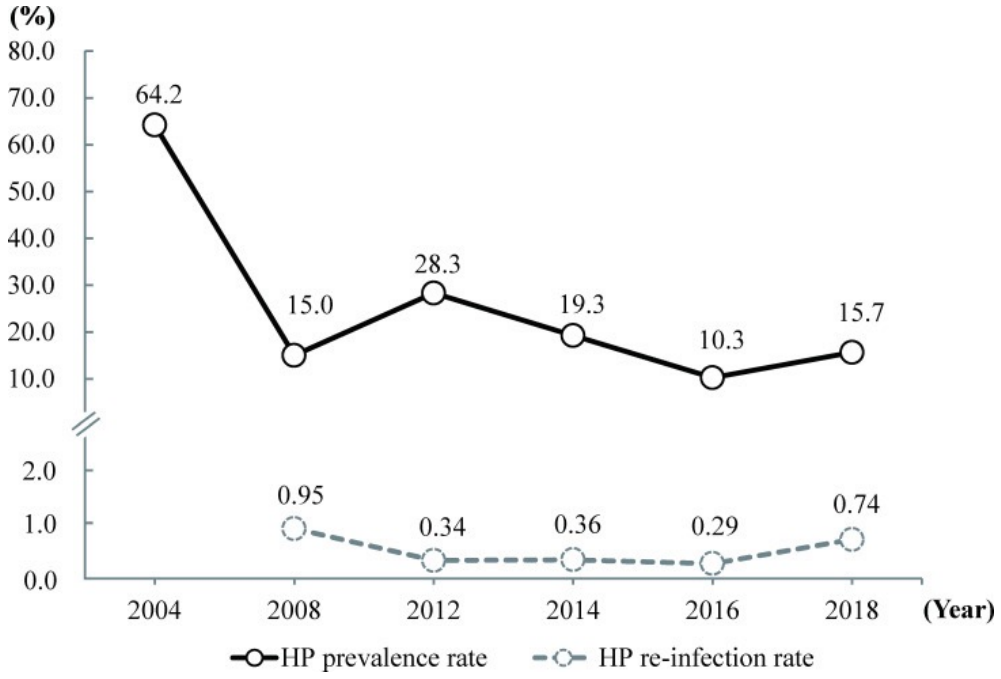
- **Apply existing knowledge to prevent**

– infection-associated cancer (e.g. cervical carcinoma, hepatoma **and stomach cancer**) by **preventive vaccination** (human papillomavirus and hepatitis B virus) or **other treatment** (hepatitis C virus and **Helicobacter pylori).**

Towards gastric cancer elimination

Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands

- **6 rounds of population-based screen and treat programs (2004-2018)**
- **HP prevalence 64% down to 15%**
- Reinfection rate <1% per person-year
- **atrophic gastritis and intestinal metaplasia decreased over time**
- **53% reduction in gastric cancer incidence compared with the historical control period of 1995-2003**
- No significant changes in antibiotic resistance rate



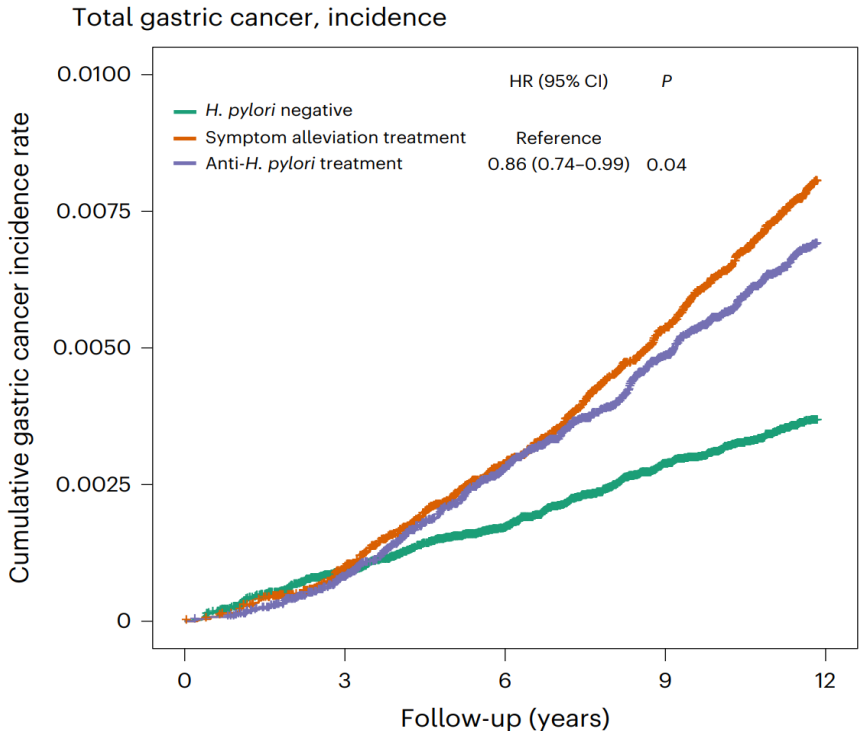
Chiang TH, Chang WJ, Chen SL et al. Gut. 2021 Feb;70(2):243-250.

nature medicine

Article https://doi.org/10.1038/s41591-024-03153-w

Gastric cancer prevention by community eradication of *Helicobacter pylori*: a cluster-randomized controlled trial

Pan KF, Li WQ, Zhang L, Liu WD, Ma JL, Zhang Y, Ulm K, Wang JX, Zhang L, Bajbouj M, Zhang LF, Li M, Vieth M, Quante M, Wang LH, Suchanek S, Mejías-Luque R, Xu HM, Fan XH, Han X, Liu ZC, Zhou T, Guan WX, Schmid RM, Gerhard M, Classen M, You WC. Nat Med. 2024 Jul 30. doi: 10.1038/s41591-024-03153-w. Epub ahead of print. PMID: 39079993.



The cluster-randomized, controlled MITS trial based on participants aged 25–54 years confirmed that H. pylori treatment reduced gastric cancer risk, albeit modestly.

Supports implementation of mass H. pylori screening and treatment from early adulthood **as a public health policy and clinical practice for gastric cancer prevention in high-risk communities**

Statement 14: Asymptomatic individuals at age above 50 years are considered vulnerable and at increased risk of gastric cancer compared with younger individuals.

Agreement 97%	Grade 1A

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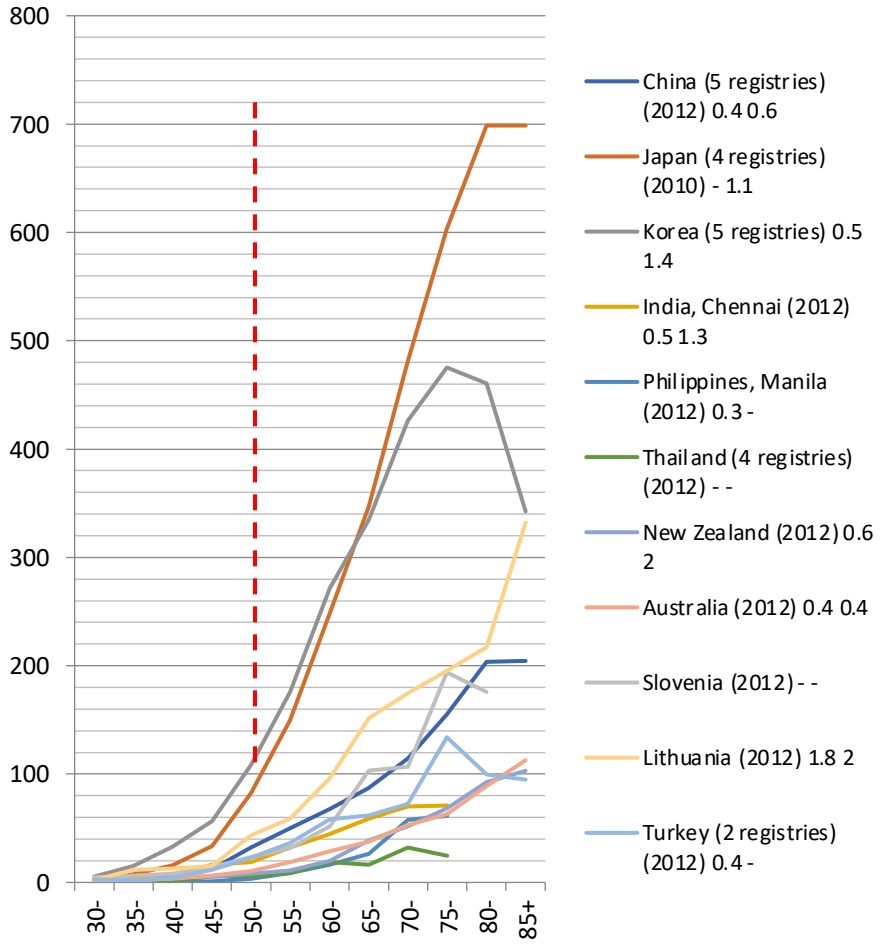
Agreement 97%

Grade 1A

The incidence of gastric cancer starts to rise substantially after the age of 50 years in the majority of countries, especially in high incidence countries.

- ***The incidence of gastric cancer was higher than 40/100,000 at the age of 50 years in high incidence countries, such as Korea, Japan, and China.***

!!! asymptomatic individuals aged 50 years or greater should be listed as higher priority for gastric cancer screening and prevention.



Global cancer Observatory (GCO). Available: https://gco.iarc.fr/ .

Malfertheiner P et al Gut. 2022 Aug 8:gutjnl-2022-327745. doi: 10.1136/gutjnl-2022-327745

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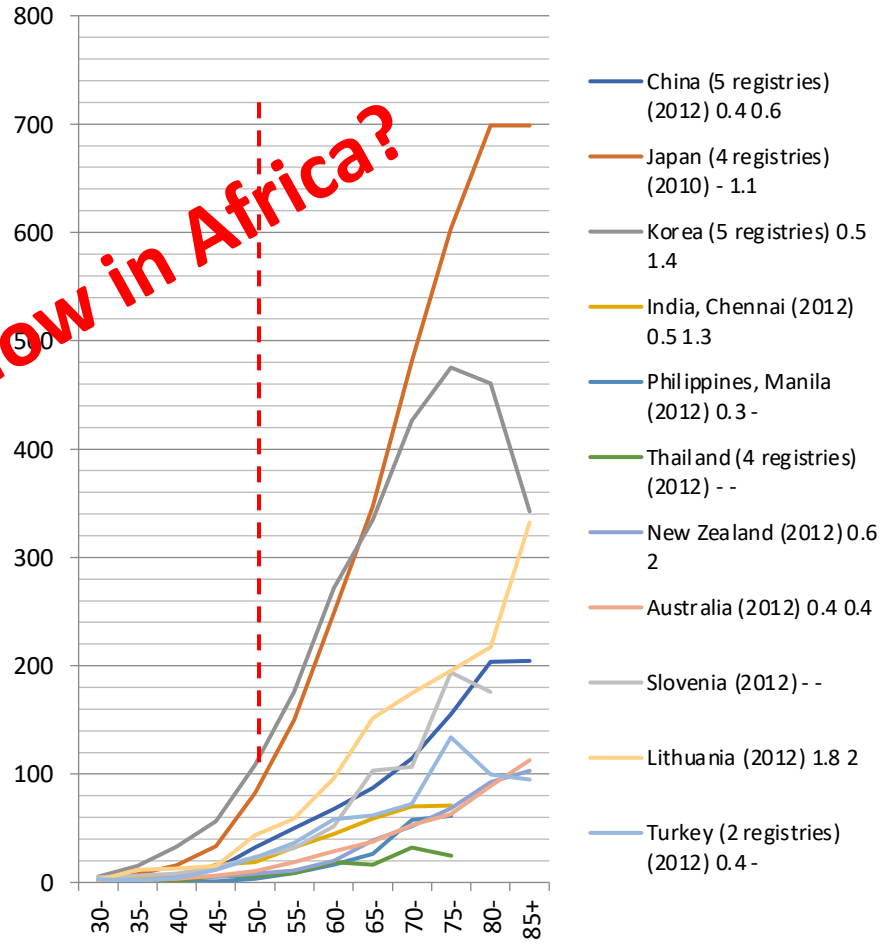


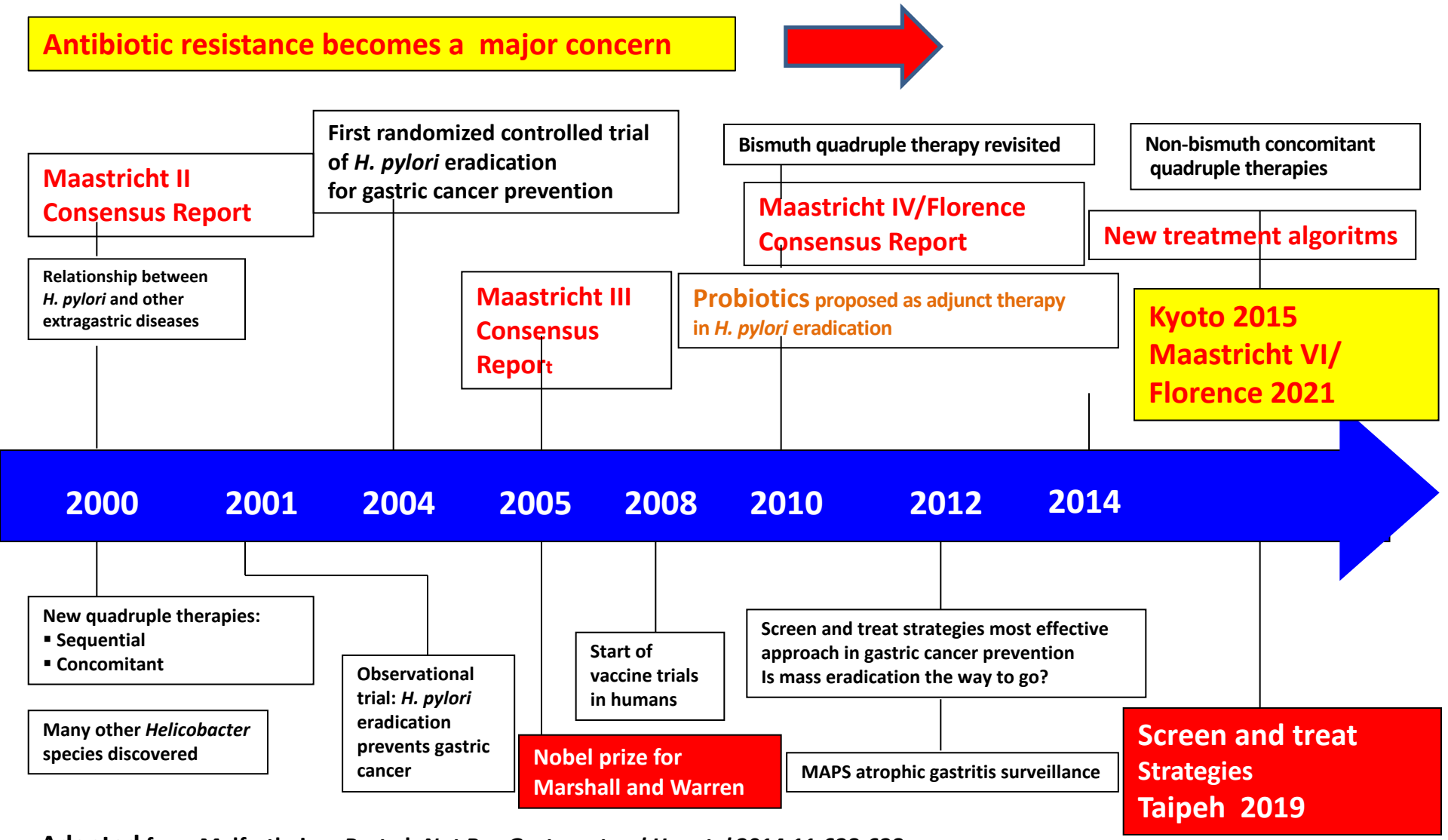
Global cancer Observatory (GCO). Available: https://gco.iarc.fr/ .

Malfertheiner P et al Gut. 2022 Aug 8:gutjnl-2022-327745. doi: 10.1136/gutjnl-2022-327745

Statement 18: Screening modalities for gastric cancer prevention (noninvasive or endoscopic) combined with colorectal cancer screening is an opportunity	
Agreement 81%	Grade C2

Timeline

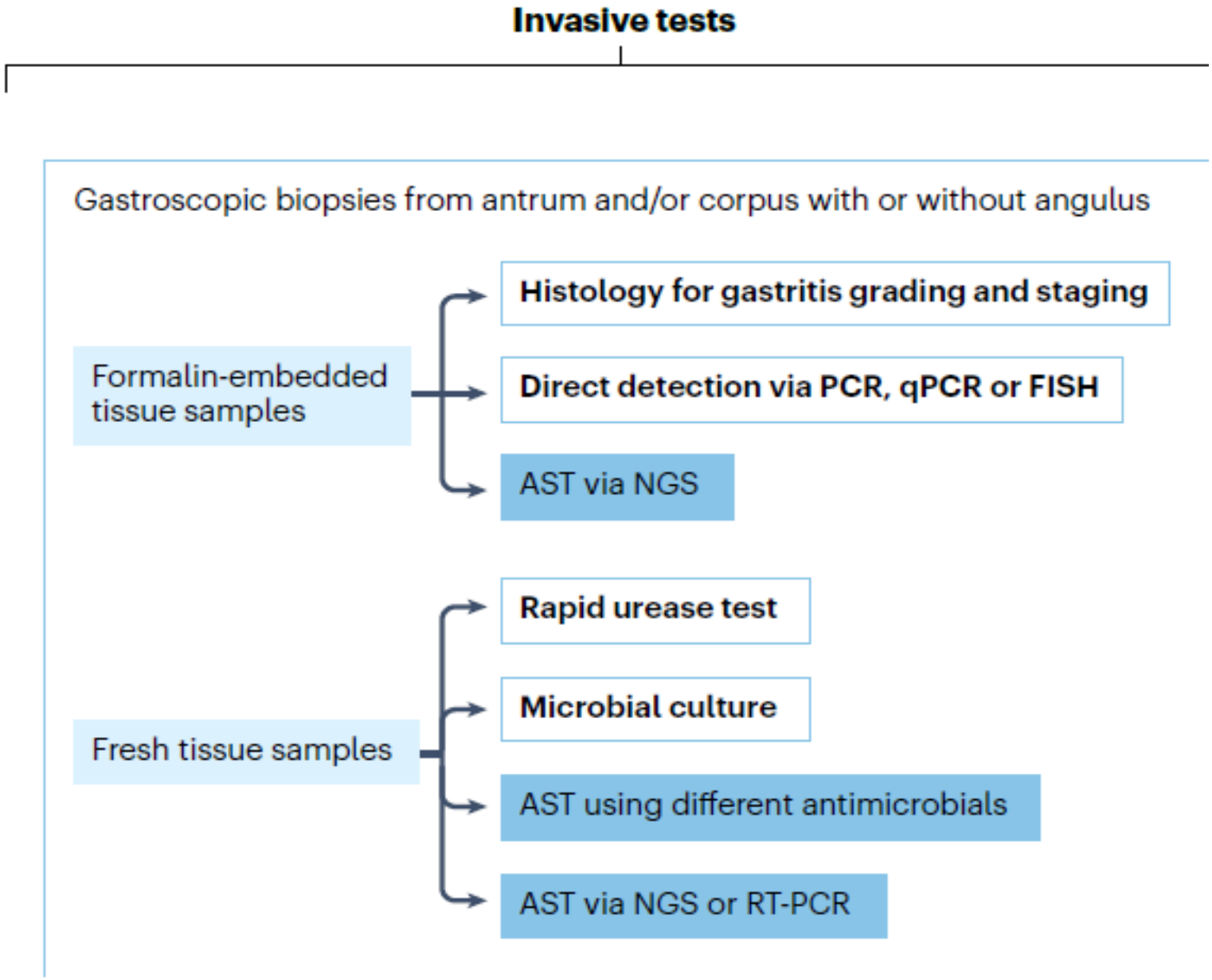
Key developments in the management of *H. pylori* since 2000

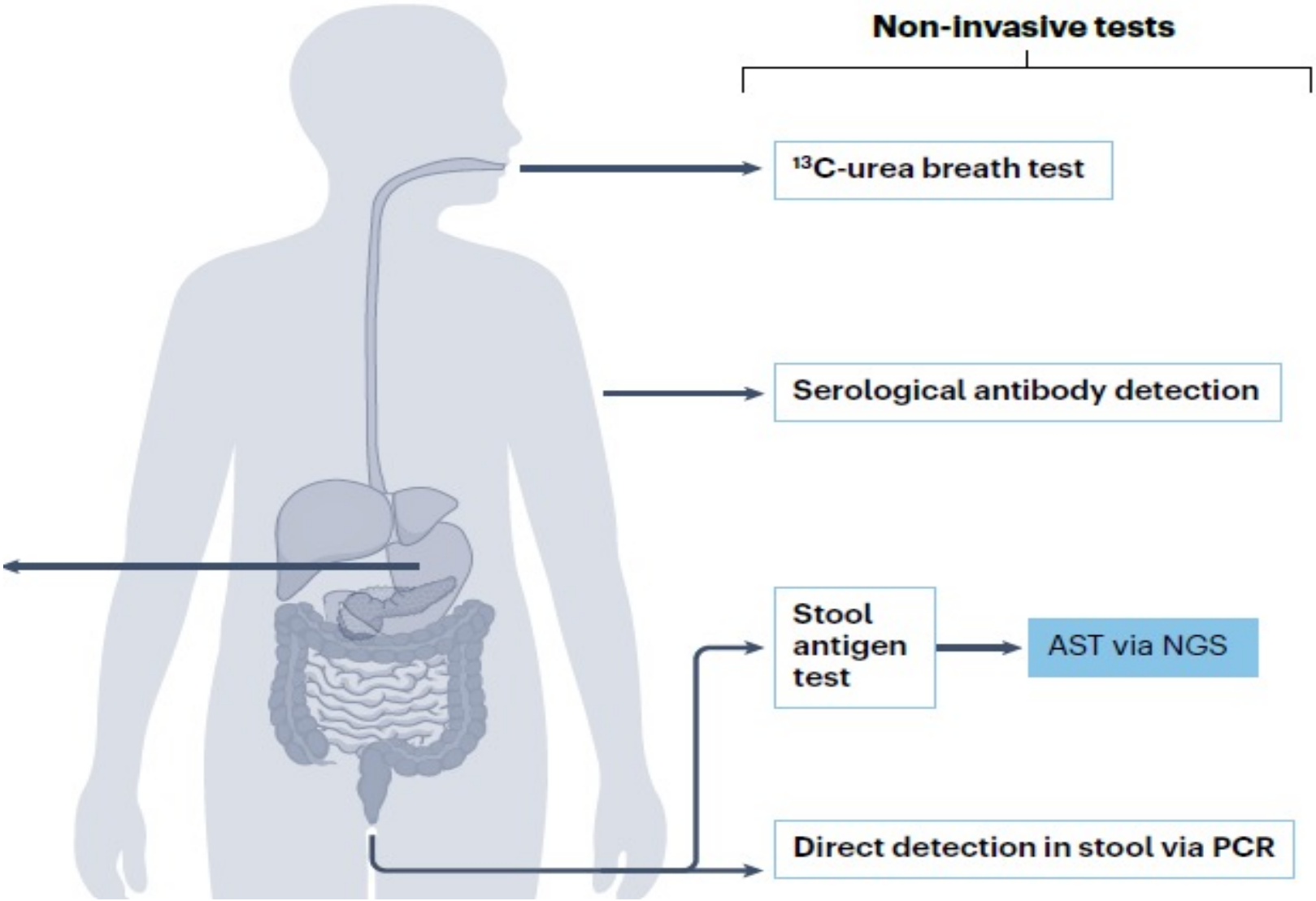


Adapted from Malfertheiner P, et al. *Nat Rev Gastroenterol Hepatol* 2014;11:628-638.

H.pylori Diagnostics

Then & NOW


Invasive tests
Gastroscopic biopsies from antrum and/or corpus with or without angulus
Formalin-embedded tissue samples
Histology for gastritis grading and staging
Direct detection via PCR, qPCR or FISH
AST via NGS
Fresh tissue samples
Rapid urease test
Microbial culture
AST using different antimicrobials
AST via NGS or RT-PCR

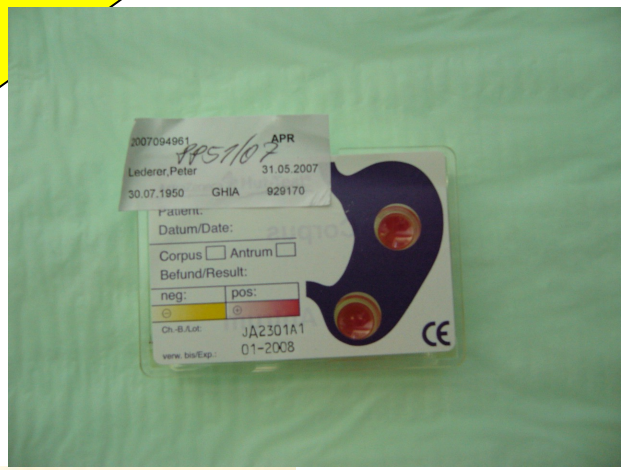


Malfertheiner P, Camargo MC, El-Omar E, Liou JM, Peek R, Schulz C, Smith SI, Suerbaum S. Helicobacter pylori infection. Nat Rev Dis Primers. 2023 Apr 20;9(1):19. doi: 10.1038/s41572-023-00431-8. PMID: 37081005.

Blood

stool

13C-UBT



H. pylori Infection

equal

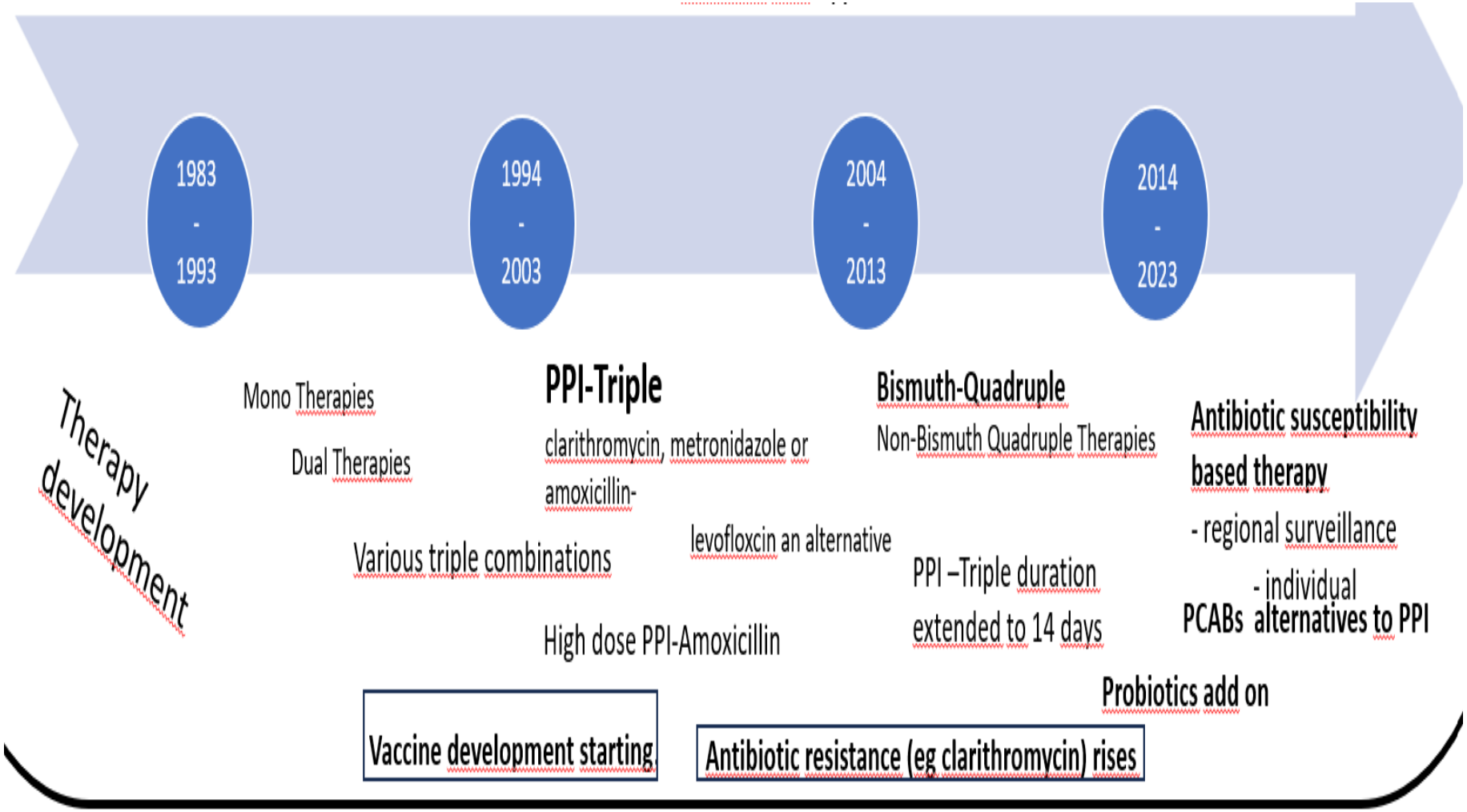
Chronic active Gastritis

= infectious disease

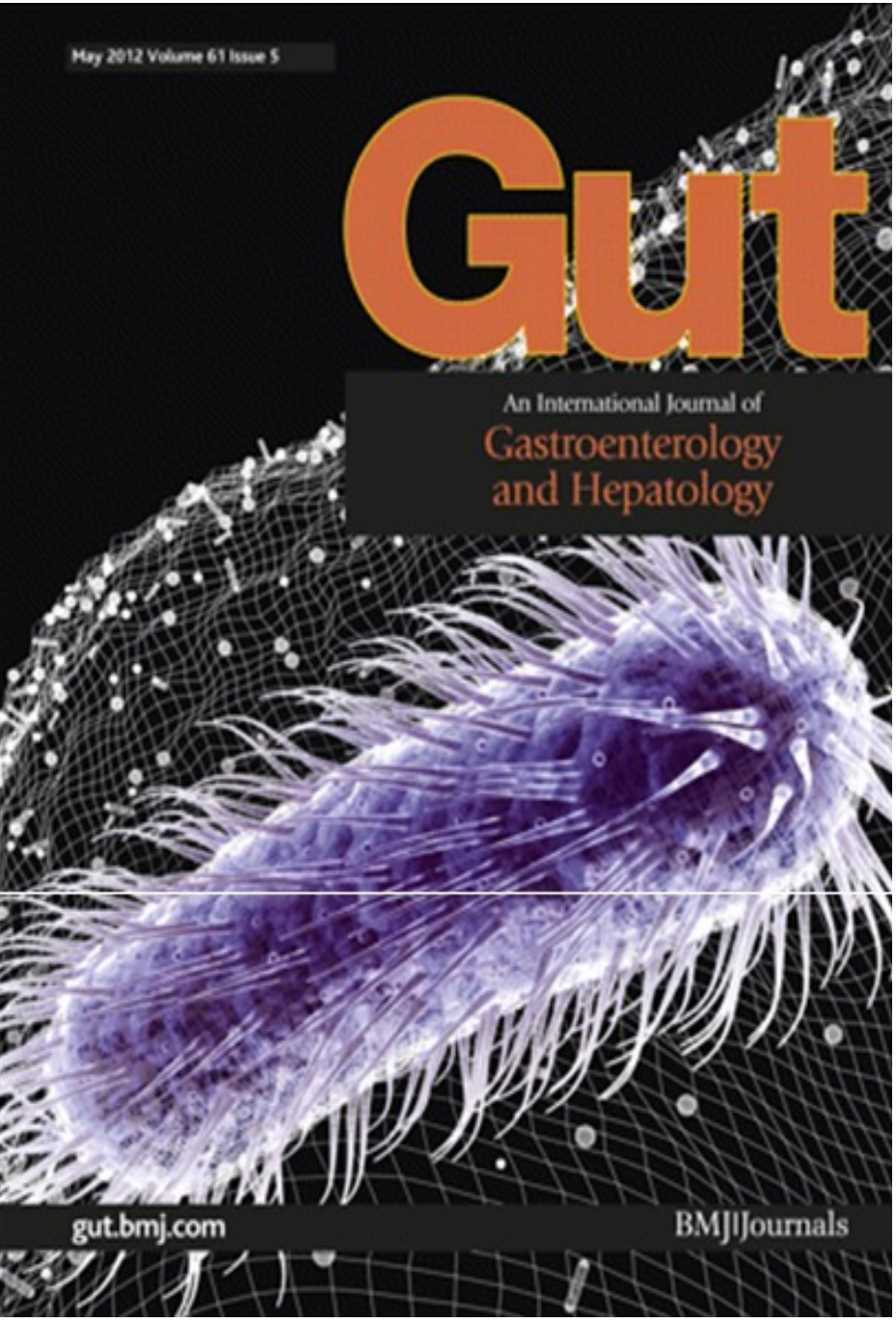
H.pylori treatment

Then and Now

Helicobacter pylori Infection: A 40-Year Journey through Shifting the Paradigm to Transforming the Management



Malfertheiner P, Schulz C, Hunt RH.
Dig Dis. 2024;42(4):299-308.



Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report

Peter Malfertheiner,[1] Francis Megraud,[2] Colm A O'Morain,[3] John Atherton,[4] Anthony T R Axon,[5] Franco Bazzoli,[6] Gian Franco Gensini,[8] Javier P Gisbert,[9] David Y Graham,[10] Theodore Rokkas,[11] Emad M El-Omar,[7] Ernst J Kuipers,[12] The European Helicobacter Study Group (EHSG)

ABSTRACT

Management of *Helicobacter pylori* infection is evolving and in this 4th edition of the Maastricht consensus report aspects related to the clinical role of *H pylori* were looked at again in 2010. In the 4th Maastricht/Florence Consensus Conference 44 experts from 24 countries took active part and examined key clinical aspects in three subdivided workshops: (1) Indications and contraindications for diagnosis and treatment, focusing on dyspepsia, non-steroidal anti-inflammatory drugs or aspirin use, gastro-oesophageal reflux disease and extraintestinal manifestations of the infection. (2) Diagnostic tests and treatment of infection. (3) Prevention of gastric cancer and other complications. The results of the individual workshops were submitted to a final consensus voting to all participants. Recommendations are provided on the basis of the best current evidence and plausibility to guide doctors involved in the management of this infection associated with various clinical conditions.

Management of *Helicobacter pylori* infection is evolving and so is our understanding of the role of the bacterium in various clinical conditions.

The European Helicobacter Study Group first took the initiative in 1996 in Maastricht to gather dedicated experts in the field and to review and discuss all relevant clinical data to arrive at recommendations for the clinical management of *H pylori* infection.[1] The Maastricht conference has since been repeated at intervals of 4–5 years.[2 3]

Aspects related to the clinical role of *H pylori* were re-examined in Florence 2010 with the Maastricht methodology. The meeting focused on indications, diagnostics and treatments of *H pylori* infection with additional emphasis on disease prevention—in particular, prevention of gastric cancer.

In the 4th Maastricht/Florence Consensus Conference 44 experts from 24 countries took active part. Experts invited were chosen for their expertise and contribution to *H pylori* research and/or guideline methodology.

METHODOLOGY AND STRUCTURE OF CONFERENCE PROCESS

Current guidelines from Japan, Asia-Pacific, North America and Europe, as well as the 'Maastricht methodology' were reviewed at an introductory plenary session.

Working groups examined the following three topics relating to *H pylori* infection:

- Indications and contraindications for diagnosis and treatment, focusing on dyspepsia, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin use, gastro-oesophageal reflux disease and extraintestinal manifestations of the infection.
- Diagnostic tests and treatment of infection.
- Prevention of gastric cancer and other complications.

Individual questions were submitted to all participants, debated and modified according to a standard template. After a thorough discussion of each statement in one of the three working groups the strength of recommendations and the strength of the supporting evidence were graded according to the slightly modified system, used in our previous report[3] (table 1). In a few statements where there are only experimental studies in support of the biological plausibility but no treatment studies, we did not quote the evidence, but graded the recommendation for the statement. For some statements the grade of recommendation did not match the level of evidence because either studies focusing on the same topic reported conflicting results or the interpretation of the studies by the experts led to a different grade of recommendation than expected from the level of evidence. Aspects related to the implementation of recommendations in daily clinical practice have also been taken into account.

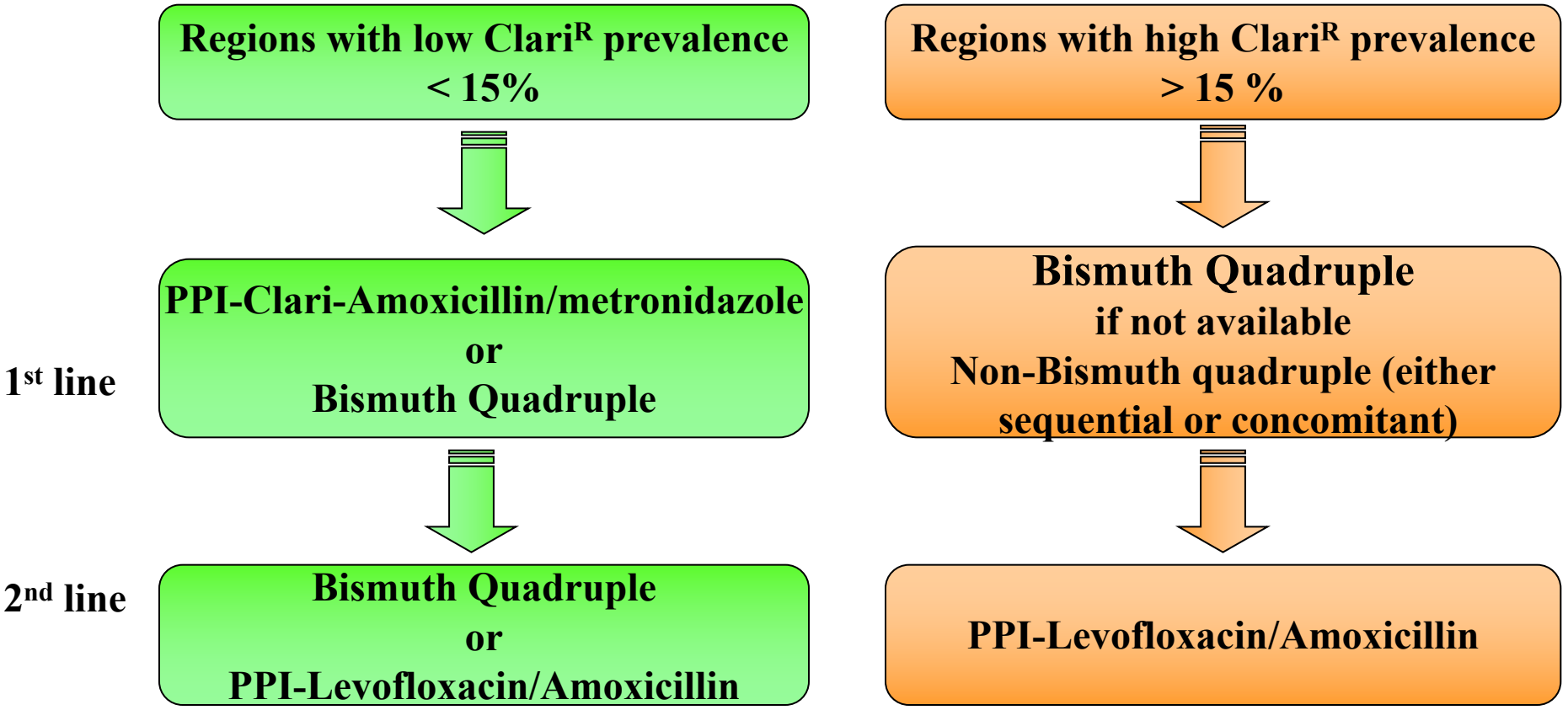
The statements and recommendations were edited and finally agreed at the concluding plenary session. Consensus was defined as support by 70% or more of the experts. The recommendations resulting from this rigorous process are reported in the manuscript.

Commentaries on statements were written by the chairmen of individual workshops based on the data presented by the person assigned to elaborate the question; they include the conclusion of discussions held at the meeting. Coauthors were involved in the final editing of the commentaries. The previous strong recommendations for *H pylori* eradication, such as in patients with peptic ulcer disease,[3] has been reconfirmed.

Gut 2012;**61**:646–664. doi:10.1136/gutjnl-2012-302084

Therapy of H.pylori Infection

Modified Malfertheiner et al. GUT 2012 May;61 (5):646-64



3rd line

Antibiotic susceptibilty testing or bismuth based quadruple combinations selected probiotics add on,rifabutin as a component, therapy duration 14 days

H.pylori treatment regimens : duration 14 days (exception 10 d)

Standard triple therapy

PPI (or P-CAB), Clarithromycin, Amoxicillin or Metronidazole

standard dose b.i.d, 500mg b.i.d., 1000mg b.i.d.(or 500mg b.i.d.)

Bismuth-containing quadruple therapy

PPI, Tetracycline, Metronidazole, Bismuth (eg Pylera ,10 days)

Standard dose b.i.d., 500mg q.i.d., 125mg q.i.d.,400 mg q.i.d.

Concomitant therapy

Concomitant therapy

PPI, Clarithromycin, Amoxicillin or Metronidazole

Standard dose b.i.d., 500mg b.i.d., 1000mg b.i.d. 500mg b.i.d.

Dual therapies

PPI high dose or P-CAB bid,

Amoxicillin, 3 times 750 mg to 1000 mg

Rescue antibiotics: Levofloxacin, Rifabutin

Parameters related to the efficacy *of H.pylori therapy*

- **Susceptibility to antibiotics**
- **Suppression of gastric acidity**
- **Life style factors**
- **Compliance /Adherence**
  - High bacterial load
  - Presence of intracellular bacteria?
- Disease entity
  - Altered immunity?

H.pylori Antibiotic Resistance

Grades of concern

high clinical concern

- **Clarithromycin**
- **Levofloxacin**

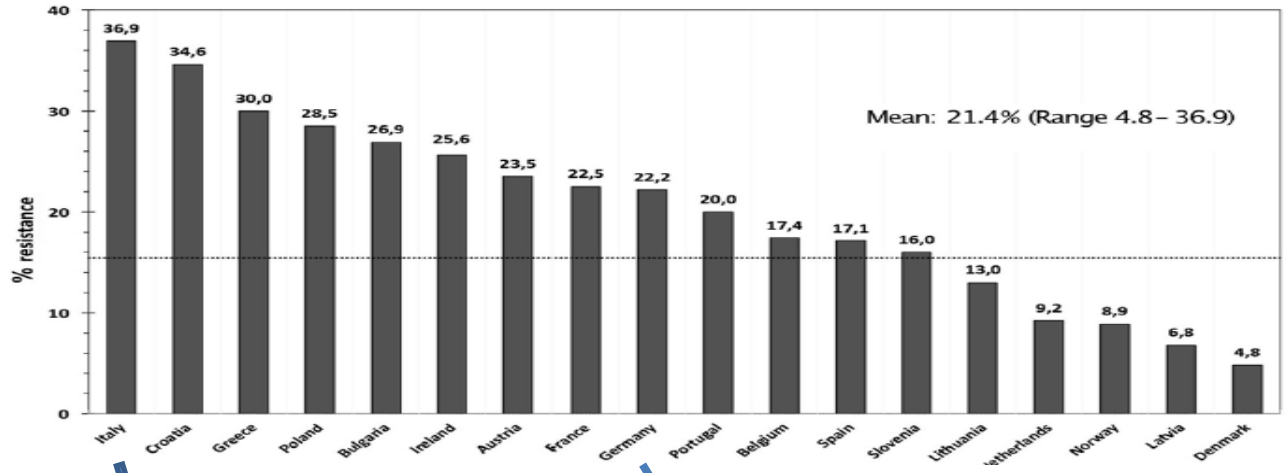
Intermediate clinical concern

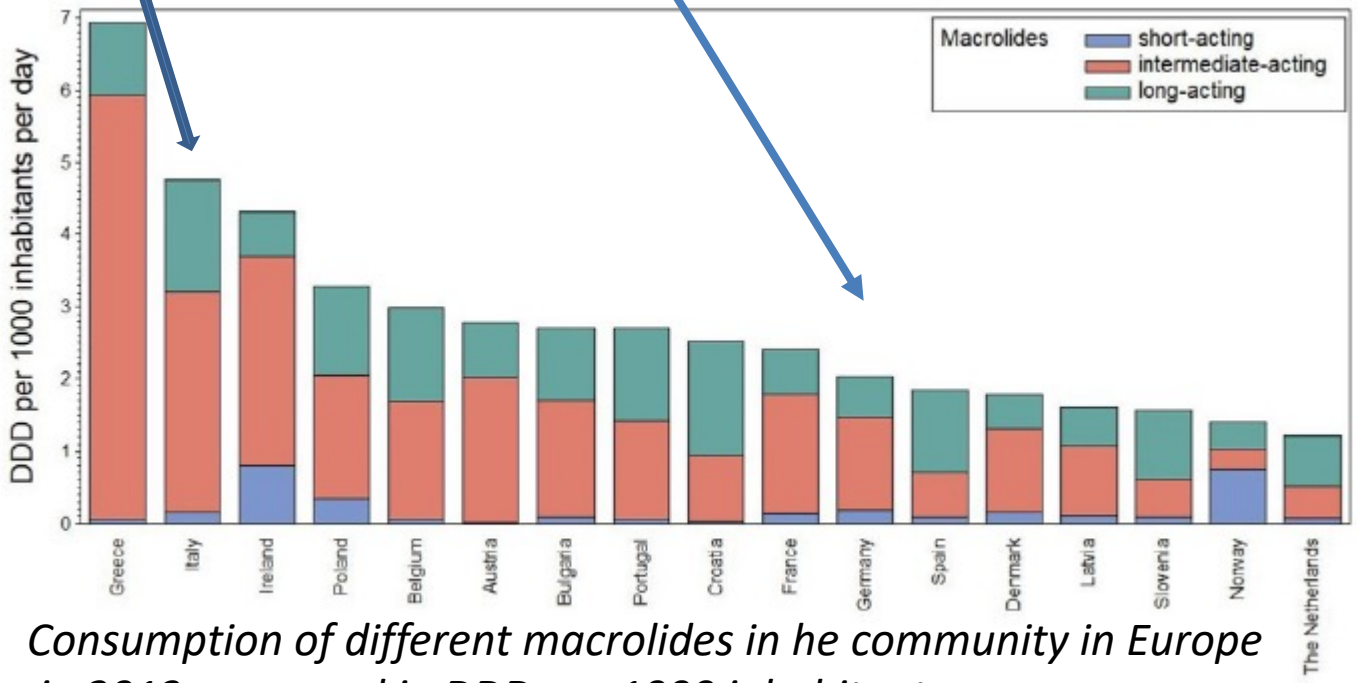
- Metronidazole

Low to no concern

- Amoxicillin
- Tetacyclin
- Rifabutin

Primary clarithromycin resistance of Helicobacter pylori in the different European countries in 2018.

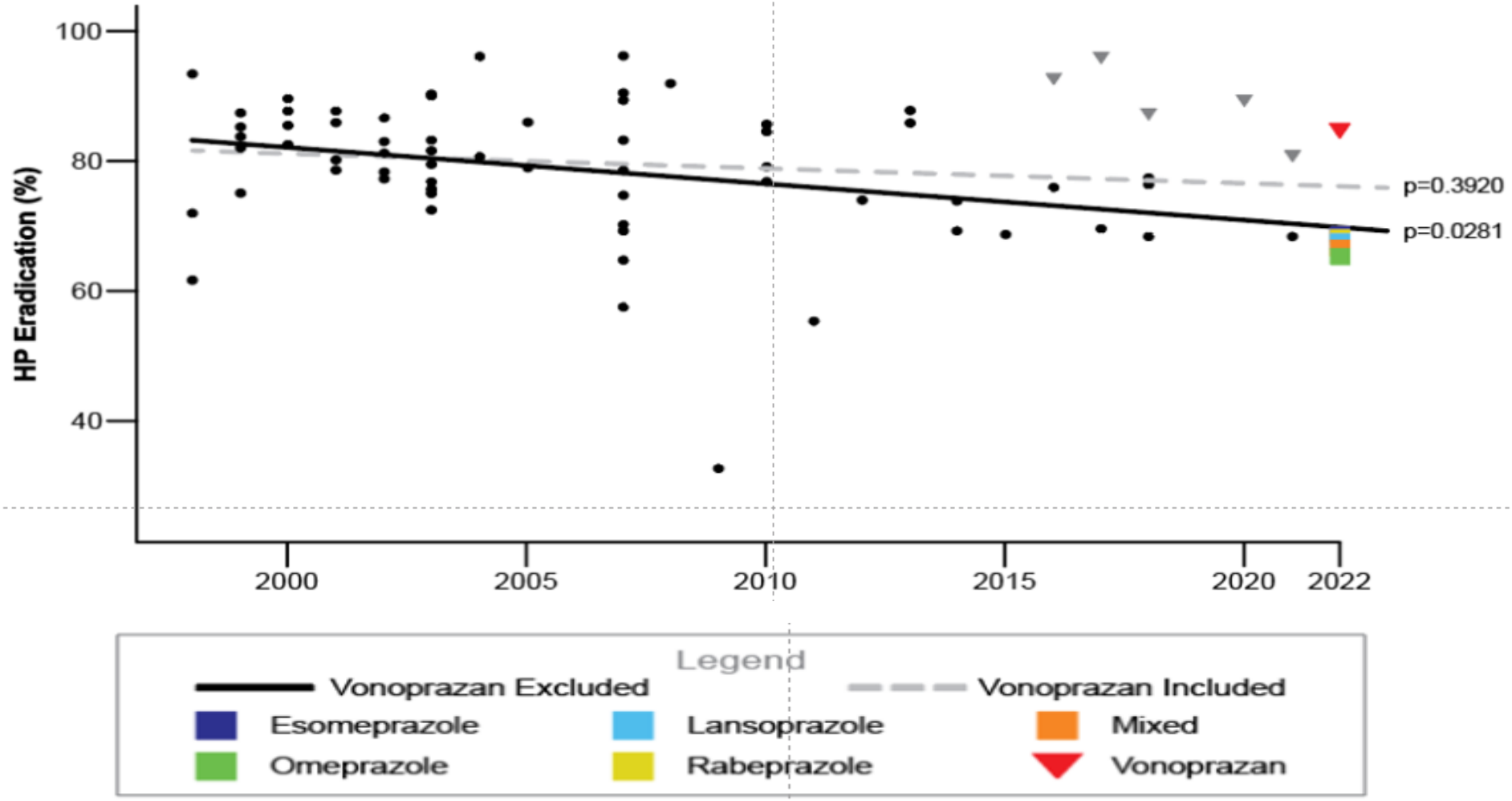




Consumption of different macrolides in he community in Europe in 2013 expressed in DDD per 1000 inhabitants
(DDD defined daily dose)

Megraud F et al. Gut 2021

H. pylori eradication rates in clarithromycin-containing triple regimens over time



Moss SF, Chey WD, Daniele P, Pelletier C, Jacob R, Tremblay G, Hubscher E, Leifke E, Malfertheiner P.. Therap Adv Gastroenterol. 2023 Jun 22;16:17562848231167284.

PPI essential for acid suppression

Gastroenterology 2021;161:1443–1459

Host Genetic Determinants Associated With *Helicobacter pylori* Eradication Treatment Failure: A Systematic Review and Meta-analysis

Shailja C. Shah,[1,2,3,4] Adam Tepler,[5] Cecilia P. Chung,[6,7] Giovanni Suarez,[3] Richard M. Peek Jr,[3] Adriana Hung,[8,9] Christianne Roumie,[8,10] and Neeraj Narula[11]

- **57 studies from 11 countries; the vast majority analyzed *CYP2C19* polymorphisms.**

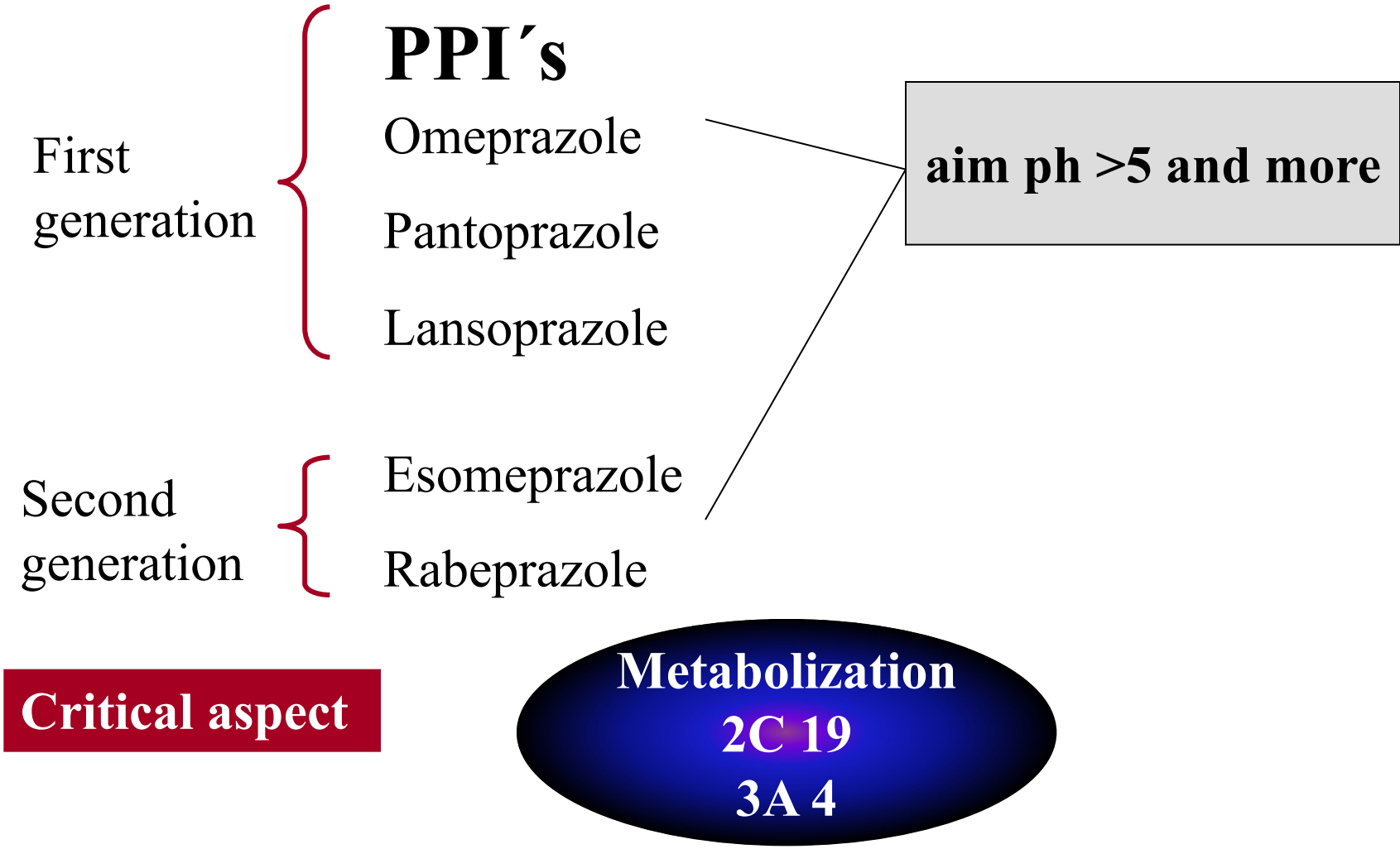
- **eradication regimens with proton pump inhibitors predominantly *CYP2C19* metabolized, enhanced vs poor metabolizer phenotypes were associated with a 2.52-fold significantly higher likelihood of eradication failure**

- and 4.44-fold significantly higher likelihood when treatment adherence and *H pylori* clarithromycin susceptibility (if relevant) were confirmed.

  - **The largest body of data support *CYP2C19* variants**

small incremental improvements in *H pylori* eradication rates would likely translate to substantial collateral health, economic, and societal benefits.

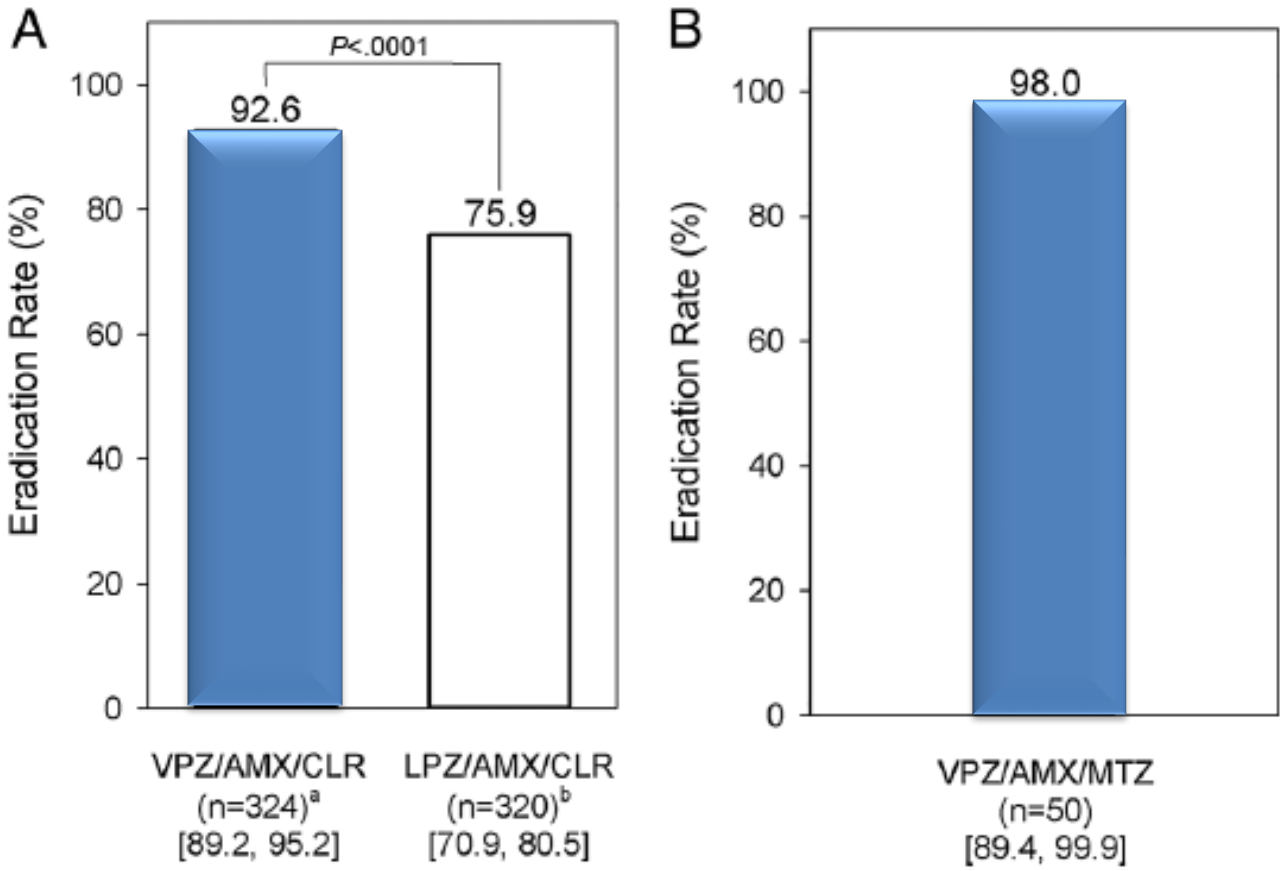
The role of acid inhibition in H. pylori eradication therapies



P-CAB Vonoprazan

H. pylori eradication rates (full analysis set) in:

A) first-line triple therapy and
B) second-line triple therapy (95% CIs shown in brackets)



Murakami K, et al. *Gut* 2016;65:1439-1446.

Gastro Hep Advances 2022;1:824–834

ORIGINAL RESEARCH—CLINICAL

Potassium-Competitive Acid Blocker and Proton Pump Inhibitor–Based Regimens for First-Line *Helicobacter pylori* Eradication: A Network Meta-Analysis

Peter Malfertheiner,[1,2] Steven F. Moss,[3] Patrick Daniele,[4] Corey Pelletier,[5] Rinu Jacob,[5] Gabriel Tremblay,[4] Elizabeth Hubscher,[4] Eckhard Leifke,[5] and William D. Chey[6]

Treatment	All countries	
	N[a]	Pooled[b], % (95% CI)
Vonoprazan-based triple therapy	3	88.2 (81.4, 92.8)
Vonoprazan dual therapy	2	80.3 (74.5, 85.1)
Esomeprazole triple	12	83.3 (78.1, 87.5)
Omeprazole triple	23	78.4 (74.6, 81.8)
Lansoprazole triple	17	78.7 (71.8, 84.3)
Rabeprazole triple	15	83.7 (79.3, 87.3)
PPI + high-dose amoxicillin	3	65.6 (56.1, 74.0)
BiQT (subsalicylate)	1	70.0 (61.2, 77.5)
BiQT (subcitrate)	7	79.6 (68.2, 87.6)
RT-DR	1	83.8 (78.4, 88.0)

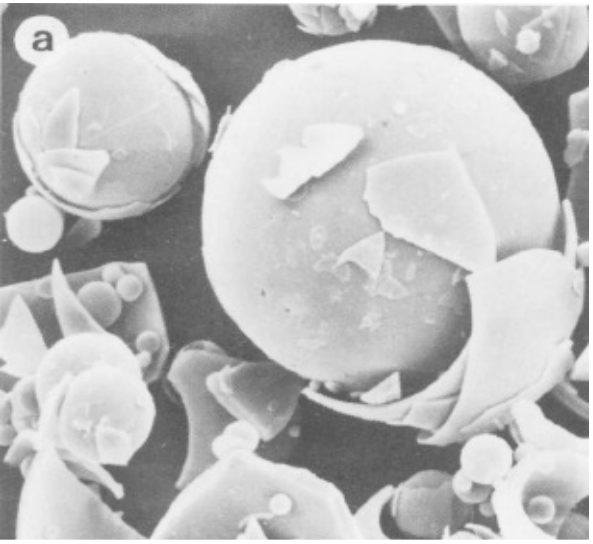
CONCLUSION:

Vonoprazan-based eradication regimens represent novel treatments for H. pylori infection on a global scale

Bismuth based therapy
Back to the Future

Bismuth based therapy:

less influenced by *H. pylori* resistance



Coghlan et al.
mono lowers DU relapses — Lancet 1987

Marshall et al.
dual renders tinidazole more effective — Lancet 1988

Rauws & Tytgat
triple cures DU — Lancet 1990

Hosking et al.
PPI + BMT — Lancet 1994

Pylera®: a new start
Laine et al. 2003; O´Morain et al. 2003

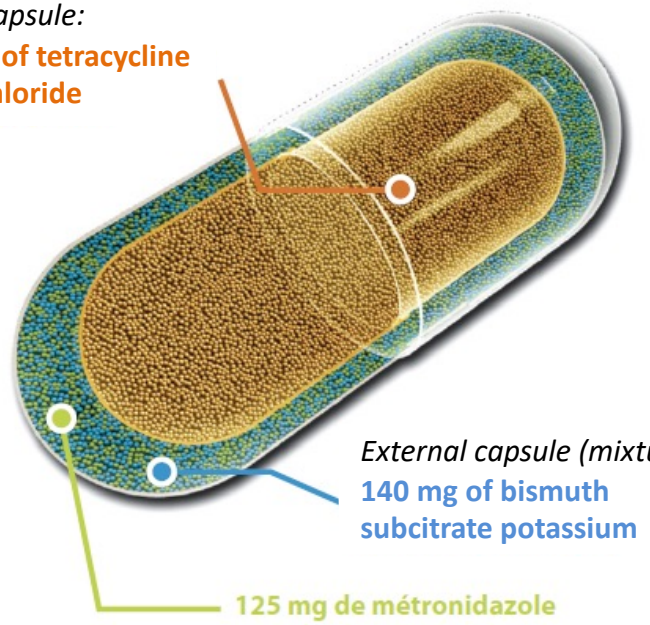
Malfertheiner et al.
Pylera overcomes resistance — Lancet 2011

An innovative galenic formulation

1 capsule, 3 active substances to fight against *H. pylori*

Inside capsule:

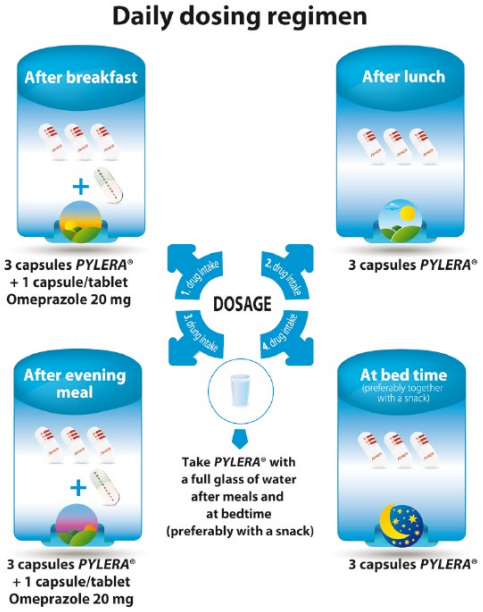
125 mg of tetracycline hydrochloride



External capsule (mixture):

140 mg of bismuth subcitrate potassium

125 mg de métronidazole



Summary of Product Characteristics. PYLERA 140 mg/125 mg/ 125 mg, gélule.

We will continue to search for solutions!!

H. pylori infection

40 years

where from now ?

Human Studies
in
H. pylori vaccine still in development

Helicobacter pylori vaccine development

Antigen candidates	Route of administration
UREASE,Ure A-Ure B	Oral
CAG A	Nasal
VAC A	Sublingual
NAP	Rectal
Bab A, Sab A, Hpa A	Parenteral
Alp A, flagellin	
…and several others	

Whole cell approach

Adjuvants always included

The only field trial

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

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*

Lancet. 2015 Jun 30

H. pylori Chinese vaccine

- **Children: age 6-15 years**
- **vaccinated with 3 doses of a fusion protein**

H. pylori* urease ß subunit plus heat labile-toxin (LTB) of *E. coli

after 1 year

2199 children vaccinated	**14 infections**
2204 children on placebo	**50 infections**

after 2 years 55% fewer new infection

Zeng et al Lancet 2015

Efficacy, immunogenicity, and safety of a parenteral vaccine against *Helicobacter pylori* in healthy volunteers challenged with a Cag-positive strain: a randomised, placebo-controlled phase 1/2 study

Peter Malfertheiner, Michael Selgrad, Thomas Wex, Benedetta Romi, Erica Borgogni, Fabiana Spensieri, Luisanna Zedda, Paolo Ruggiero, Laura Pancotto, Stefano Censini, Emanuela Palla, Niranjan Kanesa-Thasan, Bruce Scharschmidt, Rino Rappuoli, David Y Graham, Francesca Schiavetti, Giuseppe Del Giudice

www.thelancet.com/gastrohep **Published online July 2, 2018**

randomized Phase I/II, observer blind, placebo controlled, single center study

63 Helicobacter negative healthy volunteers were recruited.

- **One month after the third vaccination or placebo 34 subjects were exposed to the infectious challenge with a CagA positive *H. pylori* strain.**
- **Efficacy of protection was assessed by endoscopy based and non invasive *H. pylori* tests 12 weeks after the infection challenge.**
- **Safety and immunogenicity were monitored at preestablished regular visits.**

Challenge Tag 3-03-09

① Zacharie ② Schneiders ④ Frohne ⑥ Wichens ⑦ Rodewaldt

Tag 7 post Hp. challenge

① Nausea Tag 6 / Sdmerz
13 C-UBT neg
Fecal Antigen neg

② Tag 3-7 Nausea
13 C-UBT 4 wg
Fecal Ag ++

③ Schneiders
Tag 6-7 Nausea
Tag Ø, Erbrechen, Epig-Schmerz
13 C-UBT neg.
F-Ag +

④ keine Symptome
13 C-UBT neg
F-Ag neg

⑤ keine Symptome bis Tag 6
13 C-UBT neg
F-Ag neg.
aber Tag Ø epig. Schmerz

⑥ Tag 6-7 Nausea
Influenza-ähnliche Symptome
13 C-UBT pos
F-Ag

⑦ keine Symptome
13 C-UBT neg
F-Ag neg.

H. pylori infection at 12 weeks post challenge (V10)

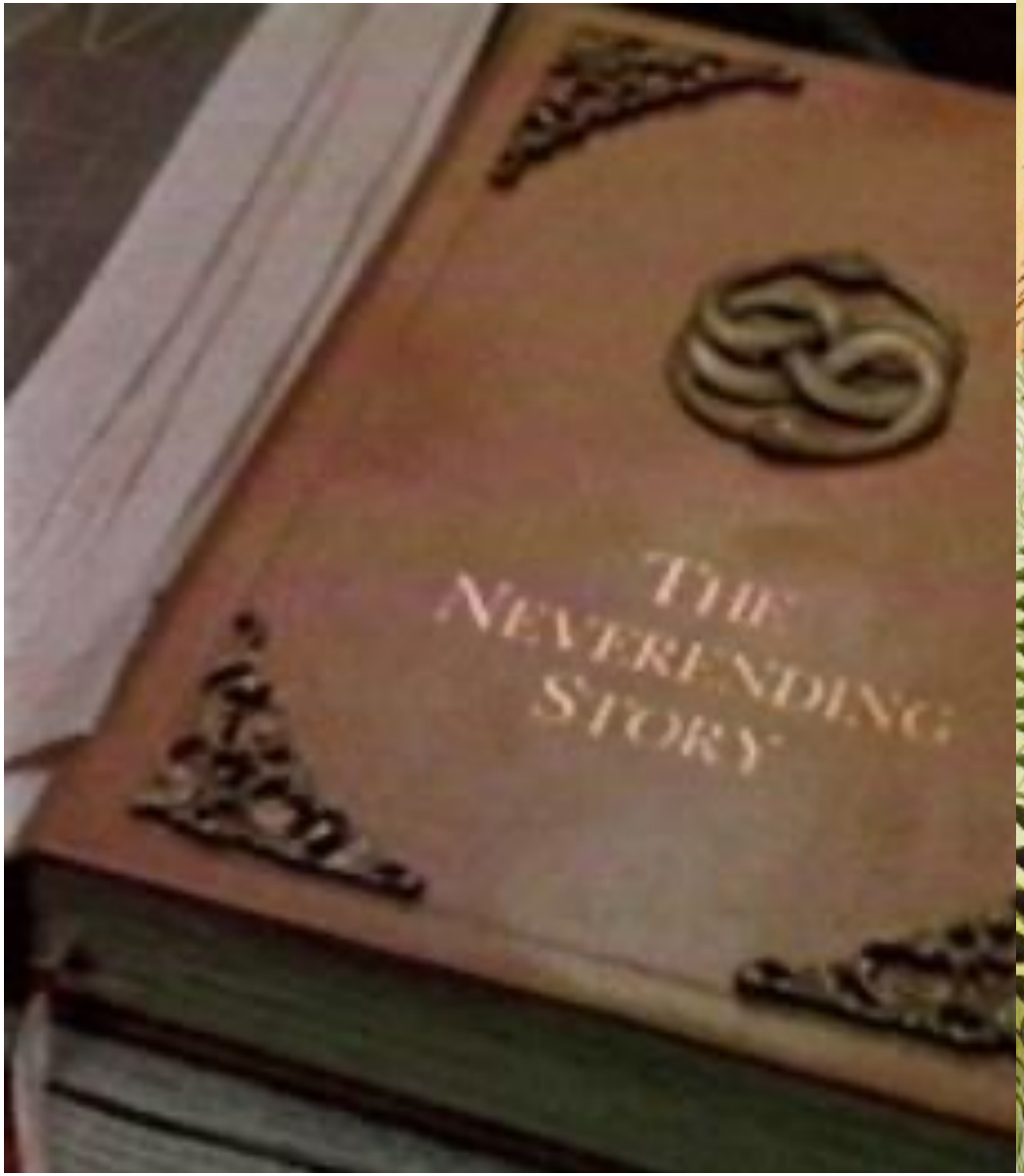
		positive	negative
Placebo	n = 15	8 (53%)	7 (47%)
IVAC	n = 19	8 (42%)	11 (58%)

NB!!! unexpected high number of negative in placebo arm

H. pylori Vaccine in humans

Summary of where we are

- **First positive results from vaccine field trial in children from China- more than a promise?**
- **Human challenge model not effective**
- **Human studies provided insight into mechanisms**
  - **-Multiple antigens/multi-epitope vaccine ?**
- Combination of different immunomodulating principles ?
  - **administration:oral, parenteral**
    - **intranasal,sublingual,(rectal)**
- **⇒ adjuvants required:different options dependent on route**



A long way to this point after 40 years

A long way ahead of us!

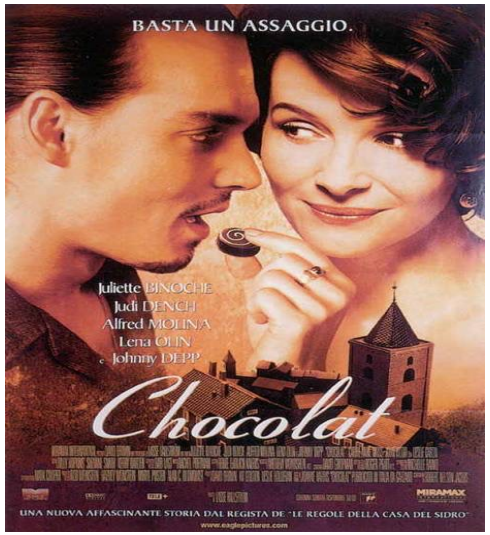
Potential therapeutic targets for non-antibiotic drugs agains *H. pylori* infection

Urease
Block the proton-gated urea channel, inhibit the activity of urease and block the production of urease.

Flagella
Inhibit motility, impair structure and production of flagella.

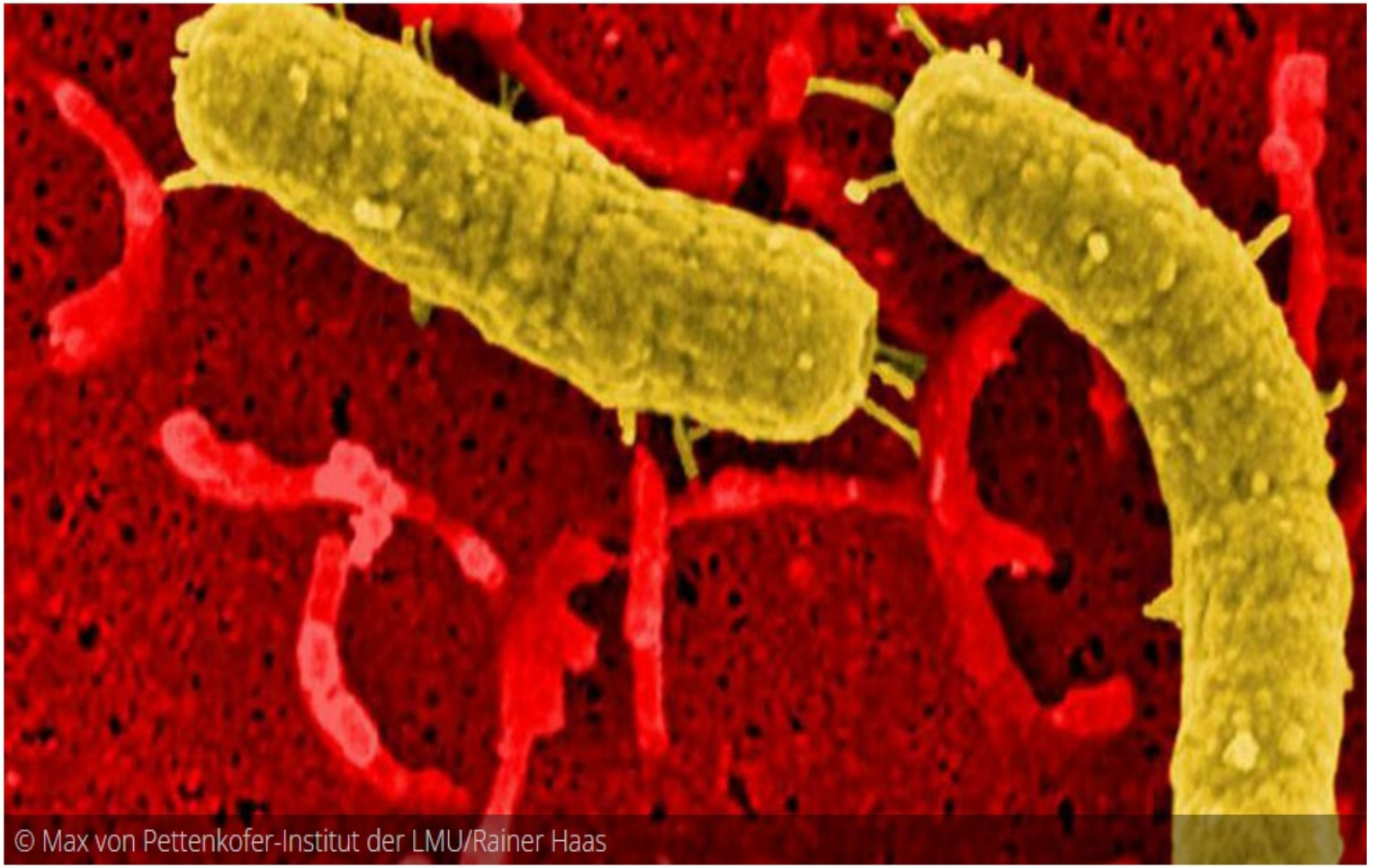
Adhesion factors
Reduce the adhesion of *Helicobacter pylori* to gastric mucosa.

Drug delivery into gastric mucus
Increase the delivery of antibiotics or new drugs into the firmly adherent mucus.



Candidates from Probiotic Medicine

Malfertheiner P, Camargo MC, El-Omar E, Liou JM, Peek R, Schulz C, Smith SI, Suerbaum S. Helicobacter pylori infection. Nat Rev Dis Primers. 2023 Apr 20;9(1):19.



- **Mitochondrial complex I inhibitors, including well-established insecticidal compounds, selectively kill H. pylori**
- **unique composition of the H. pylori complex I quinone-binding pocket is the basis for this hypersensitivity.**

Lettl C, Schindele F, Mehdipour AR et al
Selective killing of the human gastric pathogen Helicobacter pylori by mitochondrial respiratory complex I inhibitors. Cell Chem Biol. 2023 Apr 20:S2451-9456(23)00089-2. doi: 10.1016/j.chembiol.2023.04.003. Epub ahead of print. PMID: 37100053.

2005:
- Nobel prize for Marshall and Warren
- Maastricht III/Florence Consensus Report recommends selected extragastric diseases as indications for *H. pylori* eradication

2008:
- OLGA and, since 2010, OLGIM systems to predict gastric cancer risk in histological staging of gastritis

2010:
- Bismuth quadruple therapy becomes first-line option in regions with high clarithromycin resistance
- PPI-triple therapy duration extended to 14 days
- Maastricht IV/Florence Consensus Report presents a series of innovations in management; screen-and-treat for consideration in areas/communities with high gastric cancer incidence
- First randomized controlled trials of *H. pylori* vaccines for prevention of infection start

2012:
- Management of precancerous conditions and lesions in the stomach (MAPS) guidelines for surveillance of atrophic gastritis and early gastric cancer detection

2013 onwards:
- Main trials of gastric cancer prevention with *H. pylori* screen-and-treat in general populations

2015:
- Kyoto Gastritis Consensus defines *H. pylori*-associated gastritis as infectious disease
- Maastricht V/Florence Consensus Report recommends eradication therapy in individuals with *H. pylori* infection, even if asymptomatic, to prevent infection-related complications

2016:
- Potassium-competitive acid blockers become more effective alternatives to PPIs in dual and triple therapy (first available in Japan)

2019:
- Taipei consensus on screen-and-treat for gastric cancer prevention recommends eradication therapy to be offered to all individuals infected with *H. pylori* and mass screening and eradication of *H. pylori* to be considered in populations at increased risk of gastric cancer
- MAPS guidelines update (MAPSII)

2021:
- Maastricht VI/Florence Consensus Report sets the focus on antibiotic susceptibility-based treatment, strategies in gastric cancer prevention and new insights into the relationship between *H. pylori* and gut microbiota

Helicobacter pylori infection

Malfertheiner P, Camargo MC, El-Omar E, Liou JM, Peek R, Schulz C, Smith SI, Suerbaum S..

Nat Rev Dis Primers. 2023 Apr 20;9(1):19PMID: 37081005.

Helicobacter pylori Diagnosis and Treatment in Africa: The First Lagos Consensus Statement of the African Helicobacter and Microbiota Study Group.

Smith SI, Schulz C, Ugiagbe R, Ndip R, Dieye Y, Leja M, Onyekwere C, Ndububa D, Ajayi A, Jolaiya TF, Jaka H, Setshedi M, Gunturu R, Otegbayo JA, Lahbabi-Amrani N, Arigbabu AO, Kayamba V, Nashidengo PADig Dis. 2024;42(3):240-256.

Setshedi M.
Is the Current Maastricht Consensus Report Applicable for H. pylori Management in Sub-Saharan Africa? Dig Dis. 2023;41(4):572-573.

40 years after the discovery of Helicobacter pylori: towards elimination of H pylori for gastric cancer prevention.

Liou JM, Malfertheiner P, Smith SI, El-Omar EM, Wu MS
Lancet. 2024 Jun 15;403(10444):2570-2572

A long list to do`s

Creating a unified research protocol

with input from experts in various fields

- **crucial for addressing key issues in *H pylori* research,**
- **enabling standardised implementation and informing clinical practice and public health policies.**

Through these efforts and international collaborations, advances are expected towards the elimination of *H pylori* for gastric cancer prevention in the next decade.

H.pylori in Africa

- ❑ Needs
- ❑ Challenges
- ❑ Opportunities

This is why we are all here for

Dr. JR Warren