

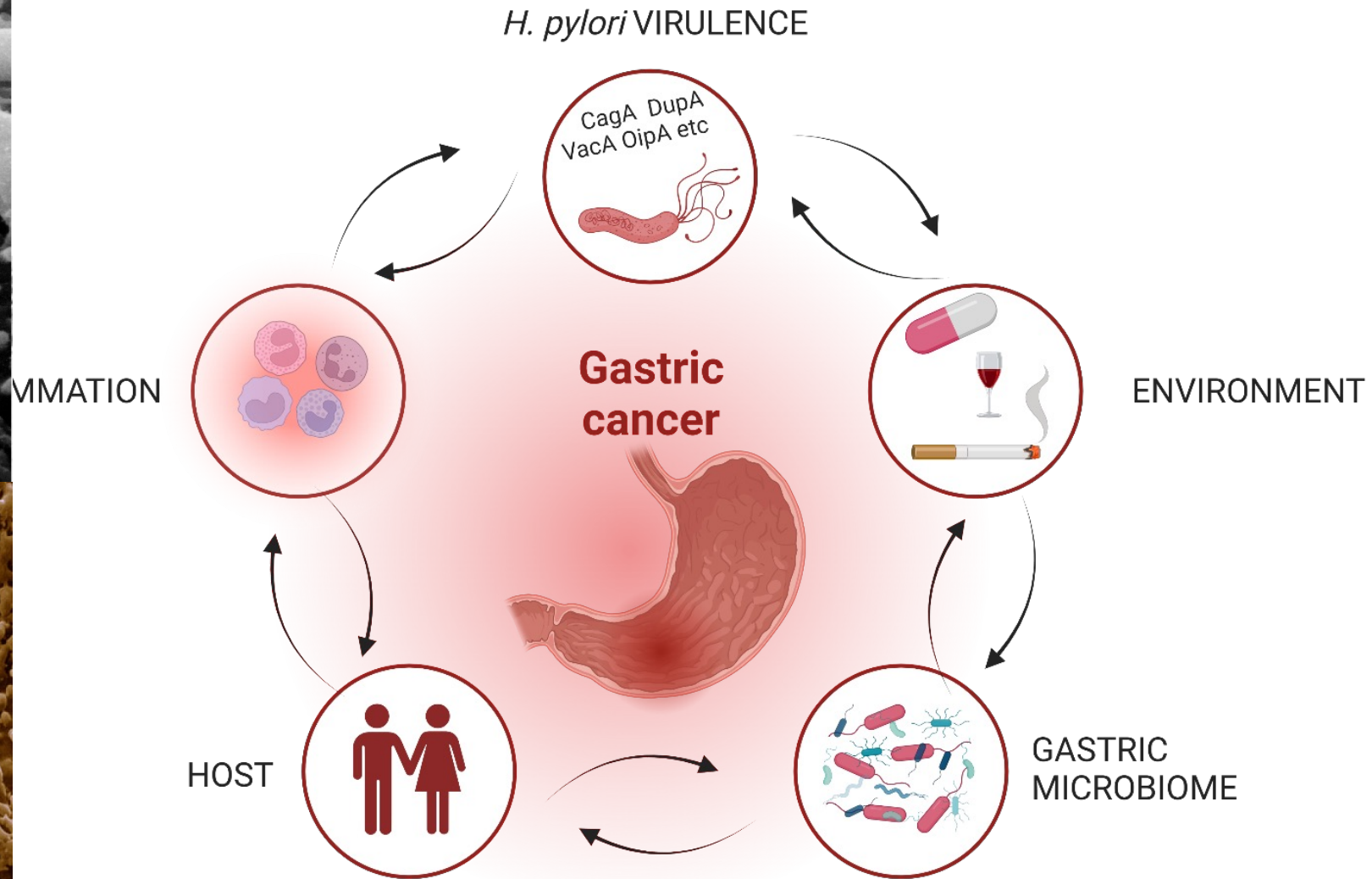
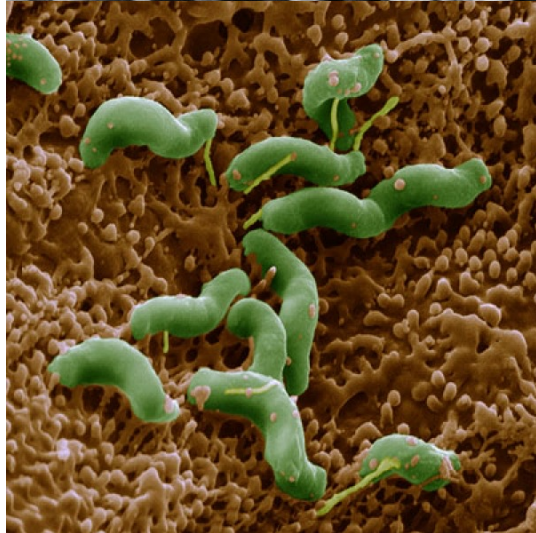
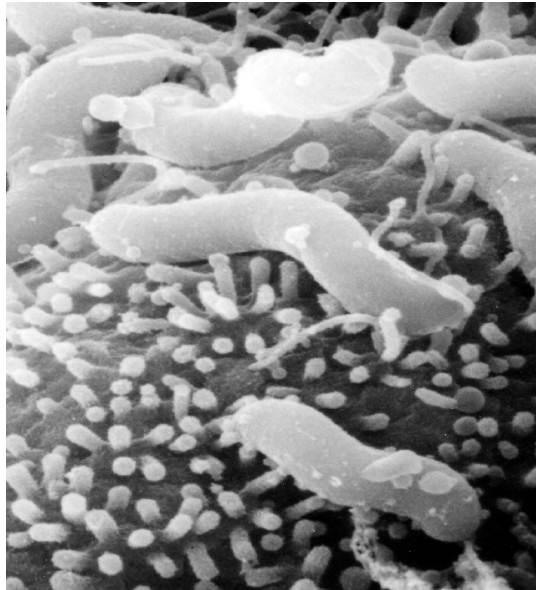
DECIPHERING THE VIRULENCE OF AFRICAN *HELICOBACTER PYLORI*: A CONTINENT-WIDE POPULATION GENETICS AND COMPARATIVE GENOMICS APPRAISAL

YOSHIO YAMAOKA

ALAIN CIMUANGA MUKANYA, EVARISTE TSHIBANGU-KABAMBA,
OITA UNIVERSITY FACULTY OF MEDICINE, OITA, JAPAN

Background: *Helicobacter pylori*

Major factors in the pathogenesis of gastric cancer

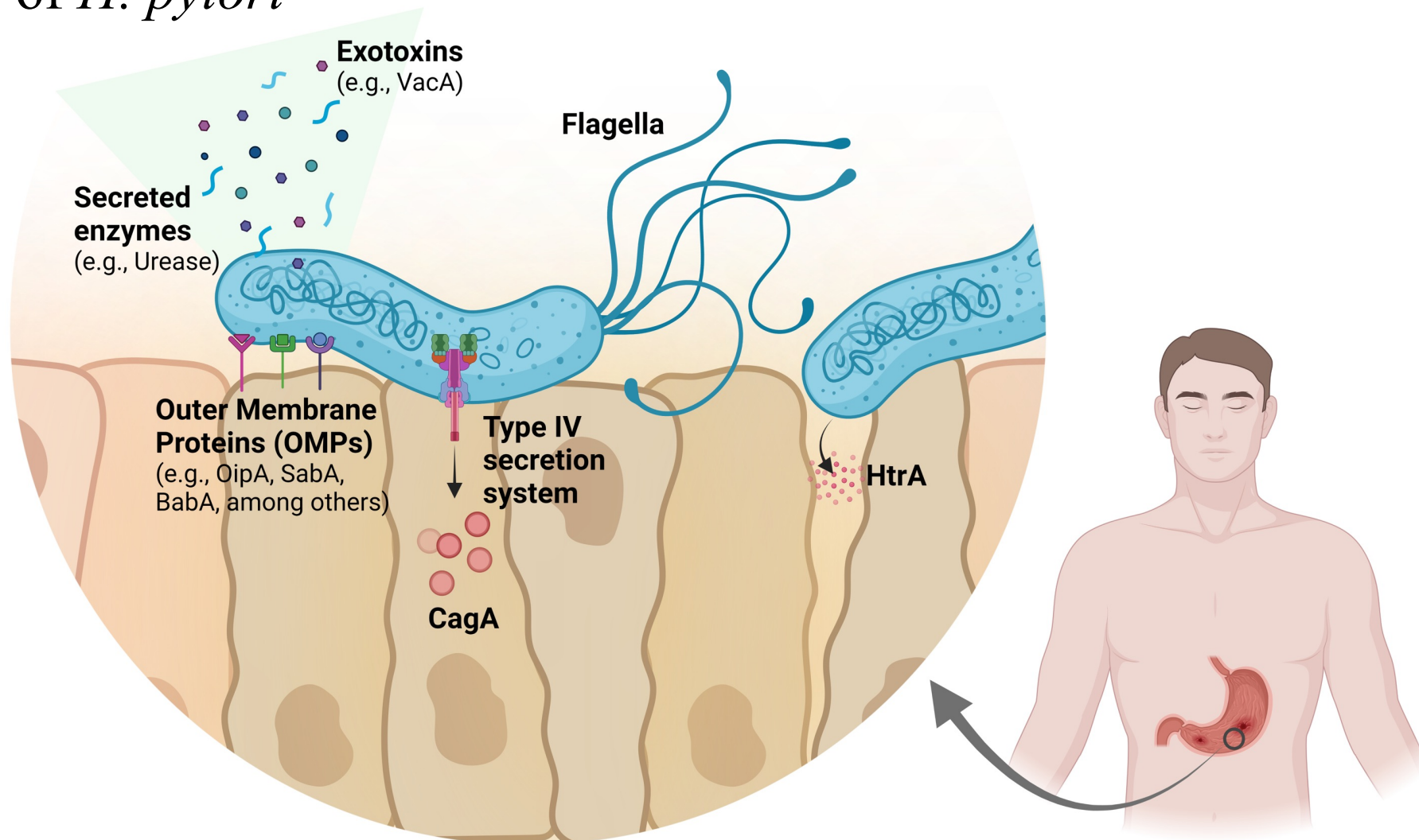


Modified from Miftahussurur M, Yamaoka Y, Graham DY. Expert Rev. Mol Med 2017

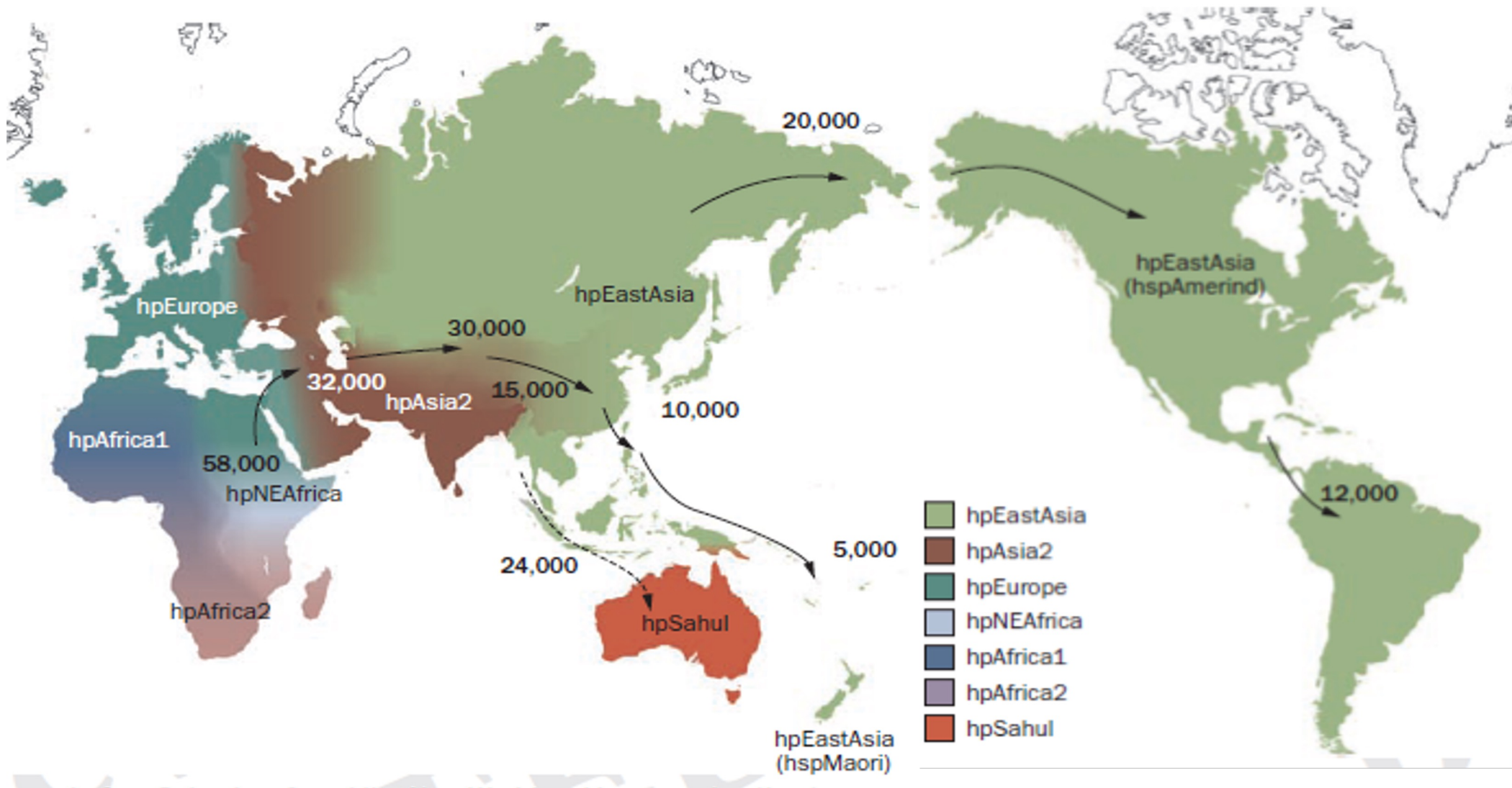
Background: *Helicobacter pylori*



Pathogenesis of *H. pylori*



Helicobacter pylori is a powerful tool to check human migration

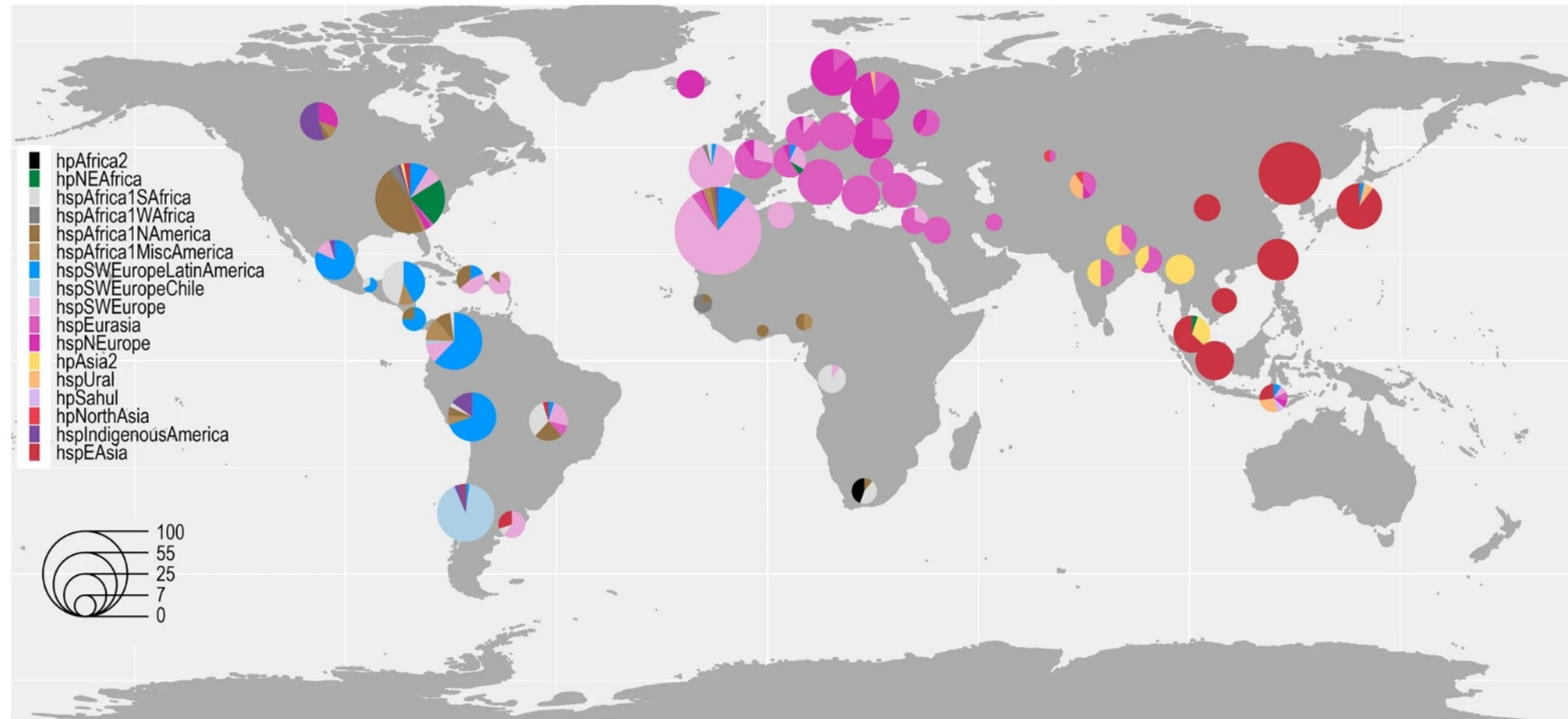


Helicobacter pylori is a powerful tool to check human migration

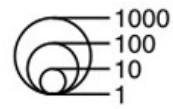
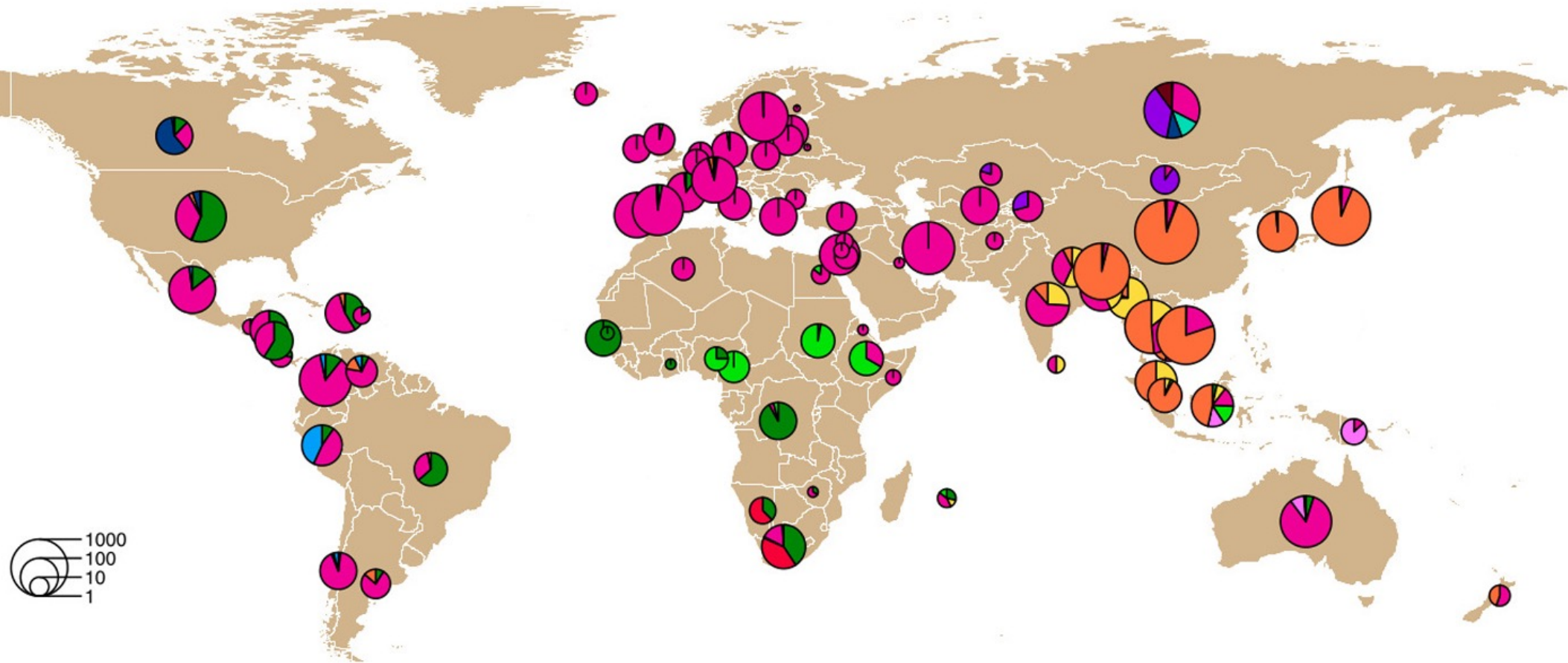


World map of *HpGP* strain origins and population assignments.

From: [The *Helicobacter pylori* Genome Project: insights into *H. pylori* population structure from analysis of a worldwide collection of complete genomes](#)

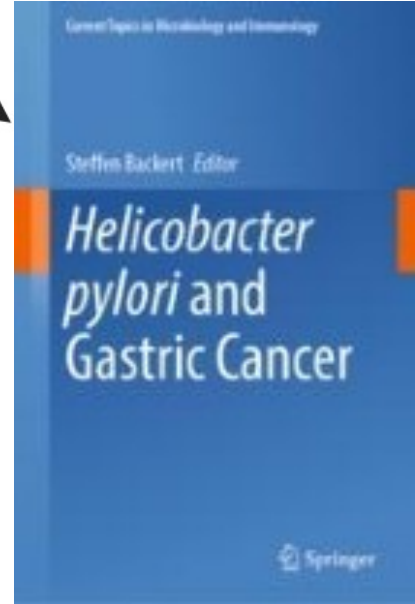
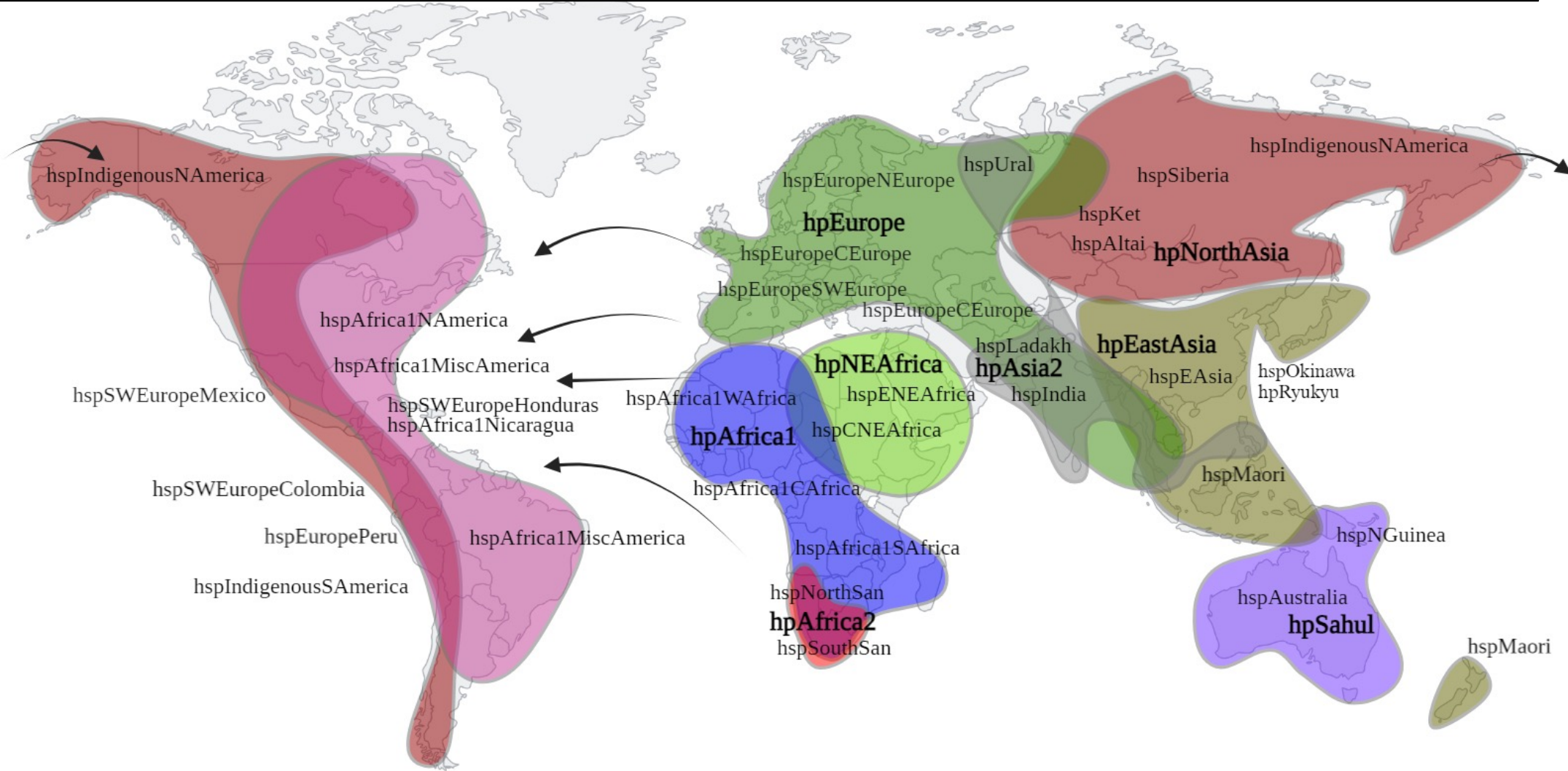


Helicobacter pylori is a powerful tool to check human migration

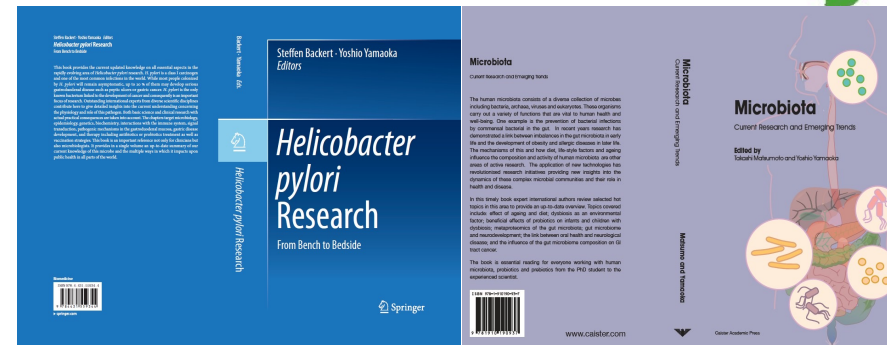


Unpublished Data

Helicobacter pylori is a powerful tool to check human migration



My Team



Department of Environmental & Preventive Medicine, Oita University Faculty of Medicine, Japan

Research Team Objectives:

My team is dedicated to conducting extensive basic and clinical research focused on *H. pylori* and related diseases, as well as exploring the broader microbiome. Our primary goals include:

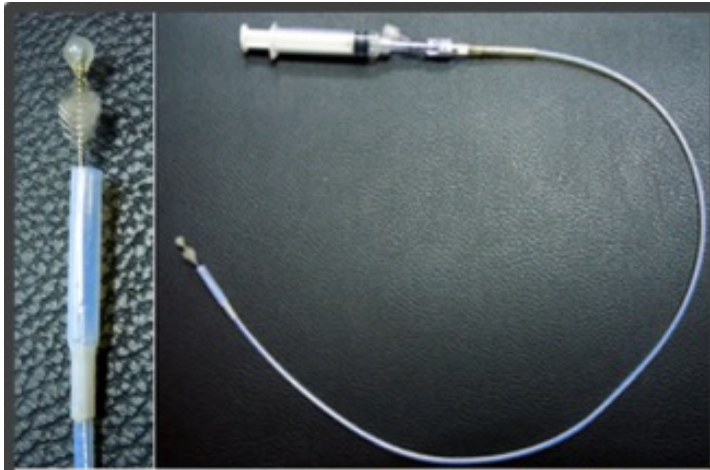
- 1) Understanding Pathogenesis:** Investigating the mechanisms by which *H. pylori* contributes to disease development, including gastric ulcers, cancer, and other gastrointestinal disorders.
- 2) Microbiome Interactions:** Exploring how *H. pylori* interacts with the gut microbiome and its impact on health and disease.
- 3) Clinical Implications:** Translating our findings into clinical applications to improve diagnostics, treatment, and prevention strategies for *H. pylori*-associated diseases.
- 4) Global Health Impact:** Extensive research to address the epidemiology of *H. pylori* and related diseases, with a particular focus on high-burden regions, such as Africa, to inform public health strategies.

EXTENSIVE COLLABORATIONS FROM ALL OVER THE WORLD



Dominican Republic

Kenya
DR Congo
Nigeria



Yoshio Yamaoka (Gastric brush)
Sulawesi Island, Indonesia



Barry J. Marshall (String test)
Aboriginal tribe, Australia



The project for institutional capacity building for eliminating *Helicobacter pylori* related death: Bhutan



Science and Technology Research Partnership for Sustainable Development [SATREPS]
(JICA + AMED project)

JICA: Japan International Cooperation Agency
AMED: Japan Agency for Medical Research and Development)

5 million US\$/5 years



Bhutanese government
(Prime Minister's office)



Khesar Gyalpo University of
Medical Sciences of Bhutan



Jigme Dorji Wangchuk National
Referral Hospital



Royal Center for Disease Control

PI: Yoshio Yamaoka



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High-end endoscopy machine to help early gastric cancer detection

March 29th, 2023 | Post Views: 648



Nima Wangdi

Oita-Khesar Gyalpo University of Medical Sciences of Bhutan (KGUMSB) gastric cancer collaborative project gifted a high-end gastroscopes machine set to JDWNRH on March 27.

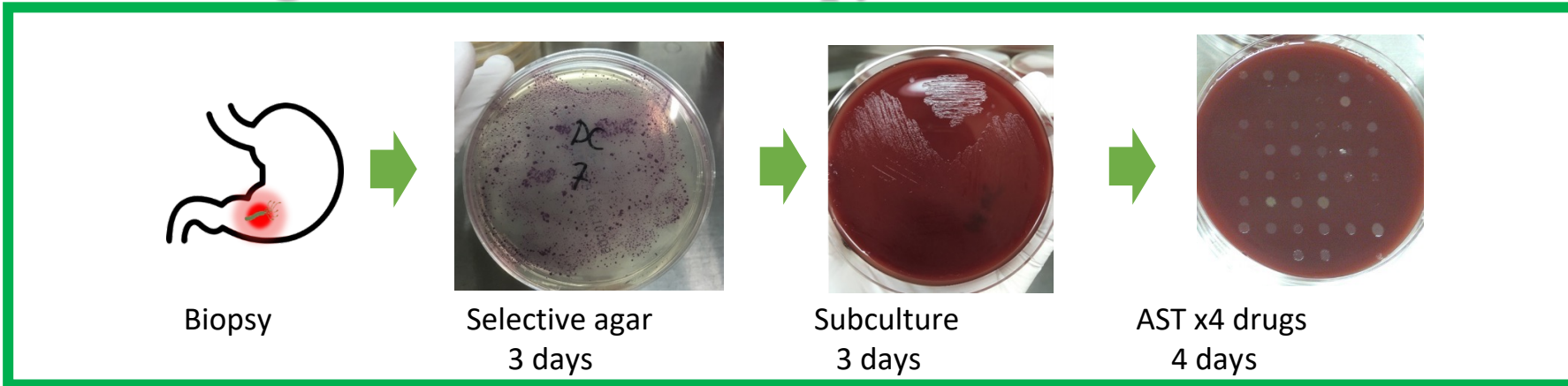
KGUMSB's Director General, Dr Sithar Dorjee said that the machine is the most advanced in the market and not many hospitals in the world have it.

He said the machine will greatly enhance the capacity to detect early gastric cancer and provide treatment on time. It will also help prevent and reduce the mortality associated with gastric cancer in Bhutan.



Sample ID	Neg (-)	CHC6	CHC14	CHC67
Test line				
Result	-	+	+	+

Teaching how to culture *H. pylori*



Introduction of culture independent AST **MIZUHO MEDY Co., Ltd.**



Collaborations between Japan and Africa ...



 研究拠点形成事業
Core-to-Core Program

B.アジア・アフリカ学術基盤形成型
B. Asia-Africa Science Platforms

 JAPAN SOCIETY FOR THE PROMOTION OF SCIENCE
日本学術振興会

 JAPAN SOCIETY FOR THE PROMOTION OF SCIENCE
日本学術振興会

 OITA UNIVERSITY
大分大学

Japan-Africa Meeting
Collaborative Research
on
Helicobacter pylori



Oita University Faculty of Medicine November 30- December 2, 2017



Oita University Faculty of Medicine November 30- December 2, 2017

Japan-Africa Meeting

Collaborative Research
on
Helicobacter pylori





CONFERENCE & LAB WORKSHOP

 OITA UNIVERSITY
大分大学

 研究拠点形成事業
Core-to-Core Program

B.アジア・アフリカ学術基盤形成型
B. Asia-Africa Science Platforms

 JAPAN SOCIETY FOR THE PROMOTION OF SCIENCE
日本学術振興会



To set up a research network between Japan and Africa



2017 Kick-off meeting

With collaborators from the DRC, Nigeria, Rwanda, and Kenya



Kinshasa Univ., DRC



Kigali, Rwanda



Nairobi, Kenya



MINI SYMPOSIUM HELICOBACTER PYLORI

-SUR ZOOM ET EN PRESENTIEL-



PR YAMAOKA

Université d'Oita/Japon & Collège
de Médecine Baylor Houston/USA



PR GANTUYA

Université Nationale
de Mongolie



DR MWANGI

Université d'Agriculture et de
Technologie Jomo Kenyatta/Kenya



PR REVATHI

Hôpital Universitaire
d'Aga Khan à Nairobi/Kenya



PR TSHIBANGU

Université de Mbuji mayi/RDC
& Université d'Osaka/Japon



PR TSHIMPI

Université de
Kinshasa



DR NGOMA

PCA Fondation Aurore
Université de Kinshasa



PR SHINDANO

Université Catholique
de Bukavu

Thème

" Traitement de l'infection à H. pylori dans le contexte
africain : une transition vers la gestion responsable
des antimicrobiens est-elle possible ? "

28 JANVIER 2023



12h00 à 17h00
(Kinshasa)



Auditorium
HJ Hospital

13h00 à 18h00
(Mbuji mayi)

Salle Polyvalente TKM
de l'INPP

13h00 à 18h00
(Bukavu)

Institut Supérieur
de Pastorale Familiale





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ACTIVITY



JOINT
RESEARCH



JOINT
USE



ACCESS



INFORMATION

Topics

2023.12.07

[FY2024 Open Call Guidelines for Joint Research,
Research Seeds has been started](#)

2023.01.13

[FY2023 Open Call Guidelines for Joint Research,
Research Seeds has been started](#)

2022.08.02

[Research Reports of FY2021 Projects\(Japanese Only\)](#)

Information

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RESEARCH CENTER FOR
GLOBAL AND LOCAL
INFECTIOUS DISEASES



JOINT RESEARCH

Call for collaboration research

To strengthen research on infectious diseases in Japan through this center; we aim to conduct joint research procedures with full-time faculty members of this center as collaborative researchers.

Along with the research themes presented by the center, we consider soliciting research themes, research meeting issues, and joint use from around the world.



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JOINT
RESEARCH



JOINT
USE



ACCESS



INFORMATION

RCGLID Awardees from African countries



2022: Nadine Keleku Lukwete

University of Mbujimayi, DR Congo

2023: Stella I. Smith

Nigerian Institute of Medical Research, Nigeria

2023,2024: Gunturu Revathi

Aga Khan University Hospital, Kenya

2024: Evariste Tshibangu Kabamba

University of Mbujimayi, DR Congo

Outcomes



Yoshio Yamaoka x Evariste Tshibangu Kabamba: 16 international journals
Yoshio Yamaoka x Gunturu Rev: 3 international journals
Yoshio Yamaoka x Stella Smith: 1 international journal

REVIEWS

 Check for updates

Helicobacter pylori infection and antibiotic resistance — from biology to clinical implications

Evariste Tshibangu-Kabamba ¹ and Yoshio Yamaoka ^{1,2} 

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

2021

Research questions in Africa



- The pathogenicity of *H. pylori* infection is profoundly influenced by the remarkable genetic diversity and geographic variation of the species, with the greatest diversification observed in Africa, where the bacterium and its human host likely originated.
- Many critical questions remain about the impact of species diversity on cell biology, pathogenicity, and clinical relevance in Africa.

H. pylori infection in Africa

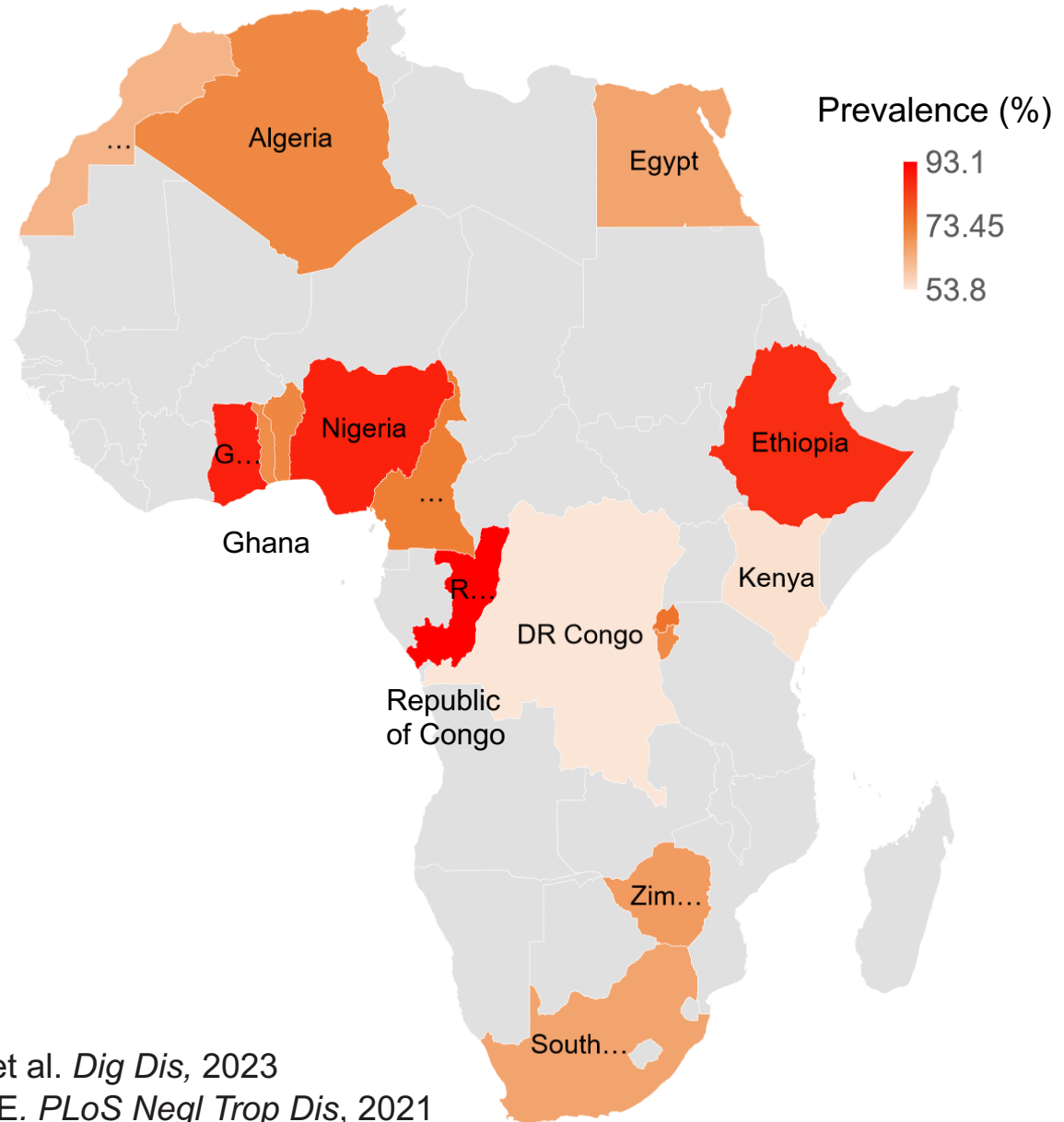


- Scarcity of data

H. pylori infection is overlooked because of other infections such as HIV/AIDS, malaria, TB, that are still big issues in many African countries

Prevalence varying :

- Population targeted
- Screening/diagnostic method
- Regions within the same country

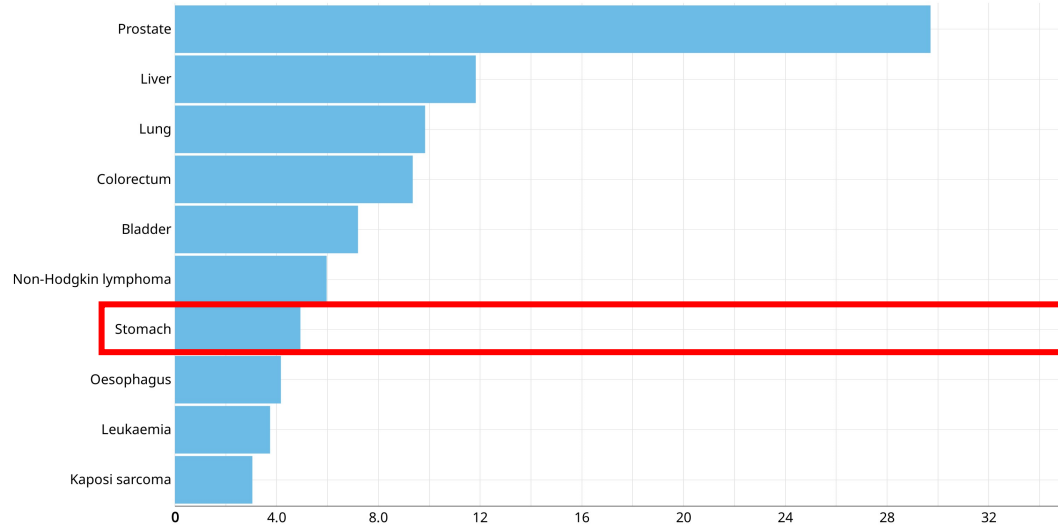


Adapted from
Stella Smith et al. *Dig Dis*, 2023
Tshibangu-K.E. *PLoS Negl Trop Dis*, 2021



Gastric cancer in Africa

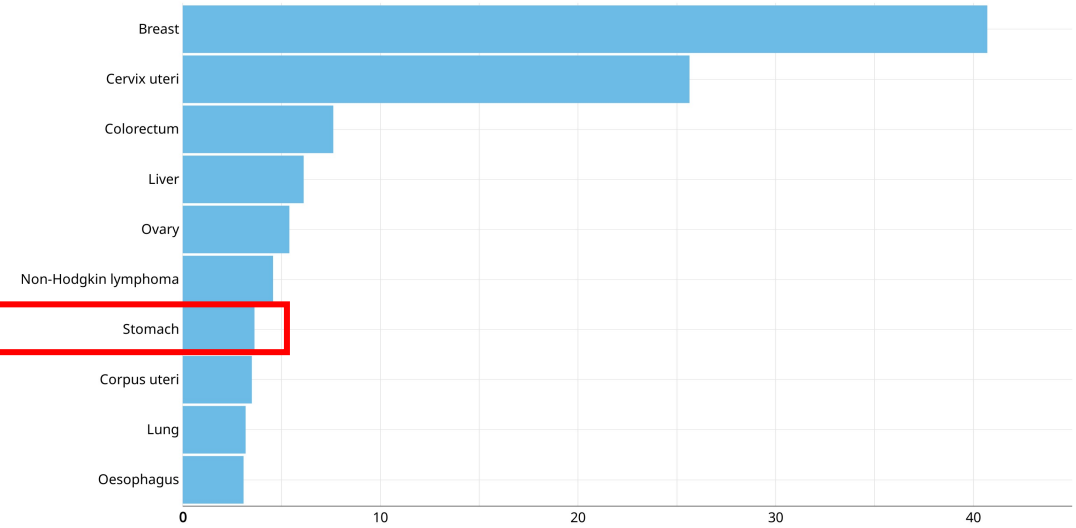
Estimated age-standardized incidence rates (World) in 2020, Africa, males, all ages (excl. NMSC)



Data source: Globocan 2020
Graph production: Global Cancer Observatory (<http://gco.iarc.fr>)

International Agency for Research on Cancer
World Health Organization

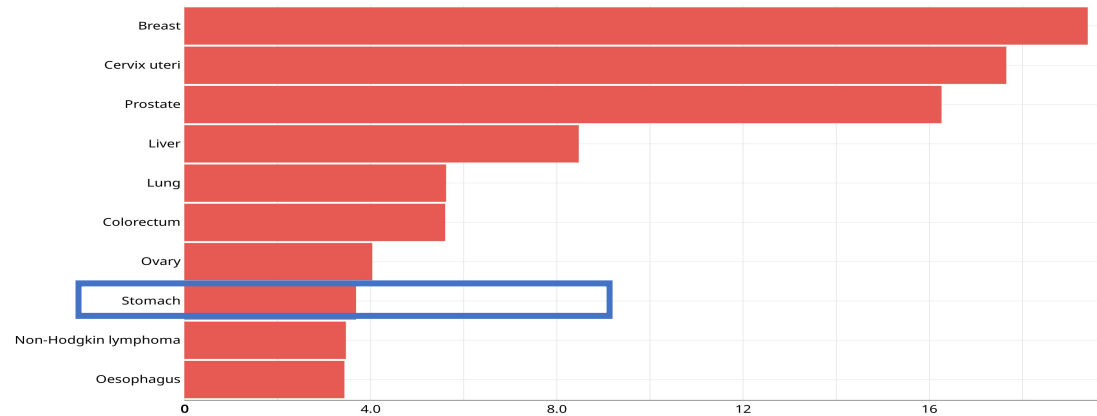
Estimated age-standardized incidence rates (World) in 2020, Africa, females, all ages (excl. NMSC)



Data source: Globocan 2020
Graph production: Global Cancer Observatory (<http://gco.iarc.fr>)

International Agency for Research on Cancer
World Health Organization

Estimated age-standardized mortality rates (World) in 2020, Africa, both sexes, all ages (excl. NMSC)

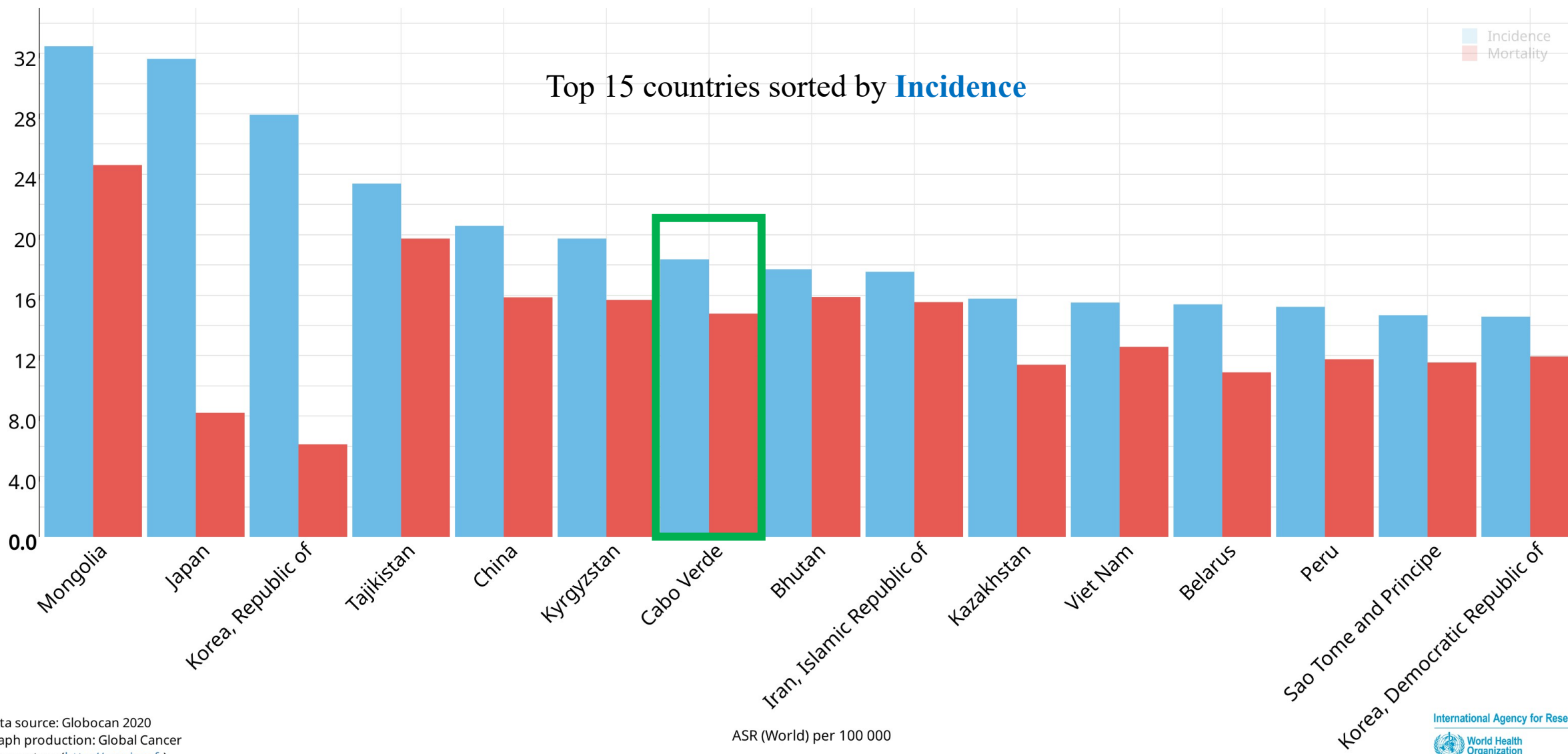


Data source: Globocan 2020
Graph production: Global Cancer Observatory (<http://gco.iarc.fr>)

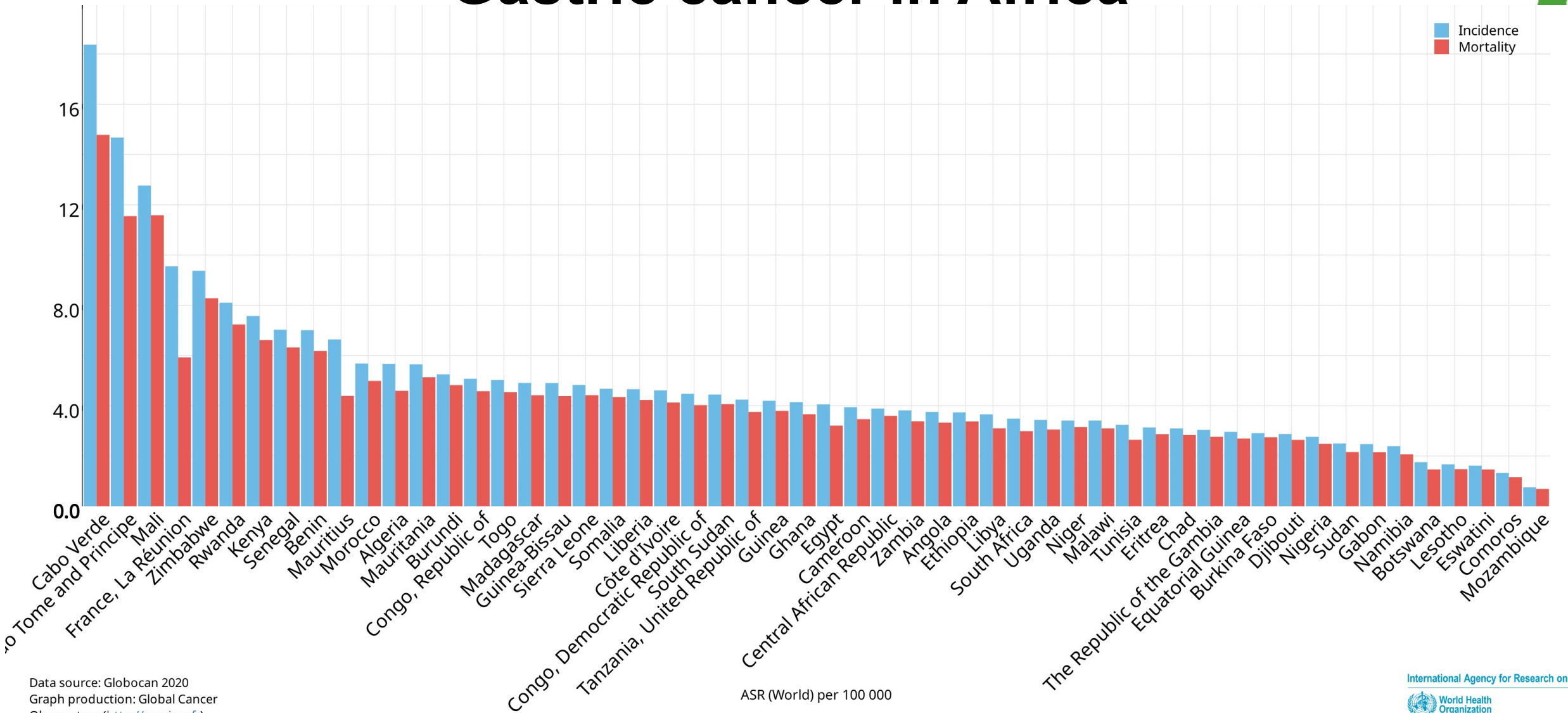
International Agency for Research on Cancer
World Health Organization

Globocan, 2020

Gastric cancer incidence and mortality in the world



Gastric cancer in Africa



Data source: Globocan 2020
 Graph production: Global Cancer Observatory (<http://gco.iarc.fr>)

ASR (World) per 100 000

International Agency for Research on Cancer





What about the so-called “African enigma”

African enigma =

A theory that actual clinical presentation/outcomes of *H. pylori* infection in African population do not correspond to expected outcomes.



Details



Journal of Digestive Diseases

Volume 10, Issue 2

May 2009

Pages 77-156

ARTICLE

African, Asian or Indian enigma, the East Asian *Helicobacter pylori*: facts or medical myths

[View article page](#)

David Y GRAHAM, Hong LU, Yoshio YAMAOKA

CITE

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<https://doi.org/10.1111/j.1751-2980.2009.00368.x>

ISSN 1751-2972

eISSN 1751-2980

Online 21 April 2009

Pages 77 - 84

Journal of Digestive Diseases 2009; 10; 77–84

doi: 10.1111/j.1751-2980.2009.00368.x

African, Asian or Indian enigma, the East Asian *Helicobacter pylori*: facts or medical myths

David Y GRAHAM,* Hong LU[†] & Yoshio YAMAOKA*

*Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas, USA; and [†]Department of Gastroenterology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai Institute of Digestive Disease, Shanghai, China

Helicobacter pylori is etiologically related to peptic ulcer disease and gastric adenocarcinomas. Reports of geographical enigmas (African, Asian, Indian and Costa Rican enigmas) are based on perceptions that clinical presentations in a population or region are not as the authors expected. We discuss the background for these enigmas and examine the evidence whether they are real or are medical myths. The African enigma was challenged almost as soon as it was proposed and recent analyses of endoscopic data have confirmed it is a myth, as *H. pylori*-related diseases occur in Africa at the expected frequencies. The Asian and Indian enigmas relate to gastric cancer and peptic ulcers, respectively, and when one takes the patterns of gastritis in the different regions, these enigmas disappear. The pattern of gastritis

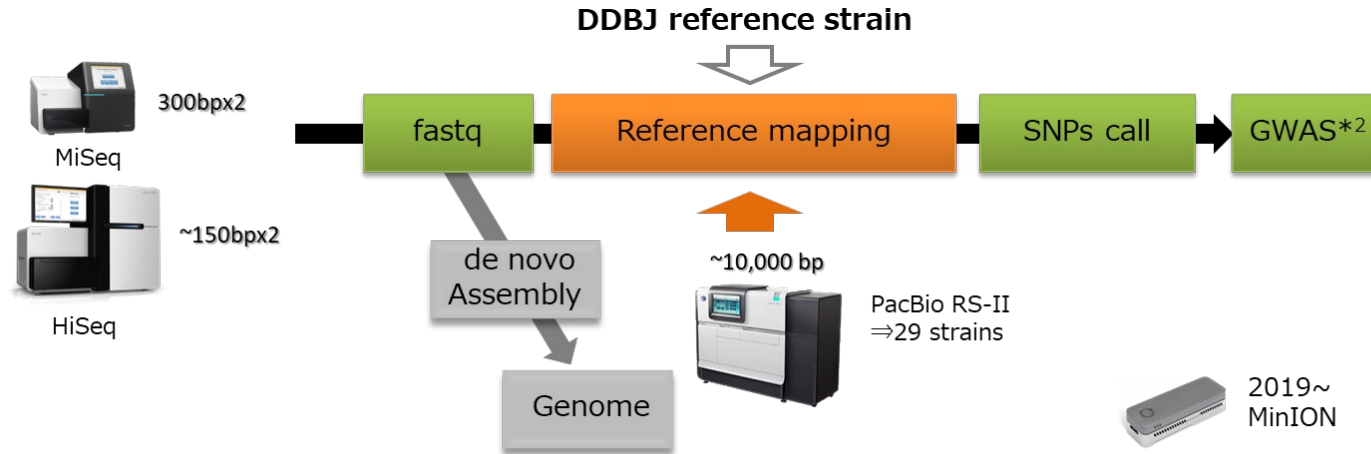
underlies and predicts the clinical outcome and the predominant pattern of gastritis has been observed to change much more rapidly than can be accounted for by changes in host genetics. There is also no evidence that these changes relate to changes in the predominant *H. pylori* strain. The factors that link most closely to preventing an atrophic corpus are environmental, with food preservation and diet currently assuming the most prominent roles. This focus on diseases (cancer vs duodenal ulcers) instead of the underlying patterns of gastritis has fostered, and possibly helped to perpetuate, these mythical enigmas. We suggest that a better strategy would be to focus on the pathogenesis of underlying histopathologic differences which could also lead to the identification of specific chemoprevention strategies.

KEY WORDS: African enigma, Asian enigma, gastric cancer, gastritis, *Helicobacter pylori*, Indian enigma, peptic ulcer.

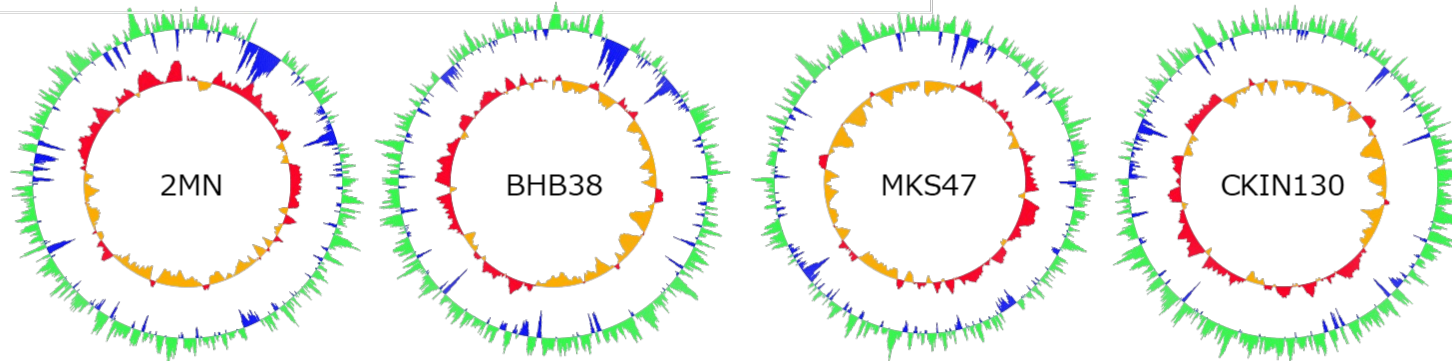
The genome of *H. pylori*



THERE ARE MORE THAN 1500 GENES IN *H. PYLORI* GENOME; SO NOVEL VIRULENCE FACTORS SHOULD BE EXISTED!!!



Genome structure of Hp (GC%, GC skew)



Outer circle: Av GC ■ High GC, ■ Low GC ⇒ Plasticity zone: cagPAI & T4SS
Inner circle: GC skew: ■ positivity (G>C), ■ negativity (C>G) ⇒ transcription start/ stop

Aims



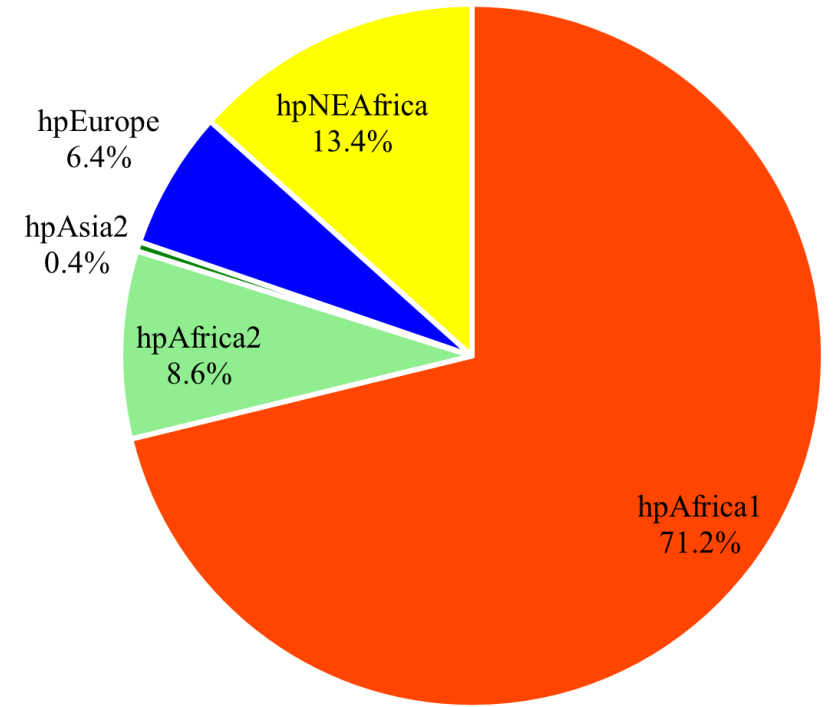
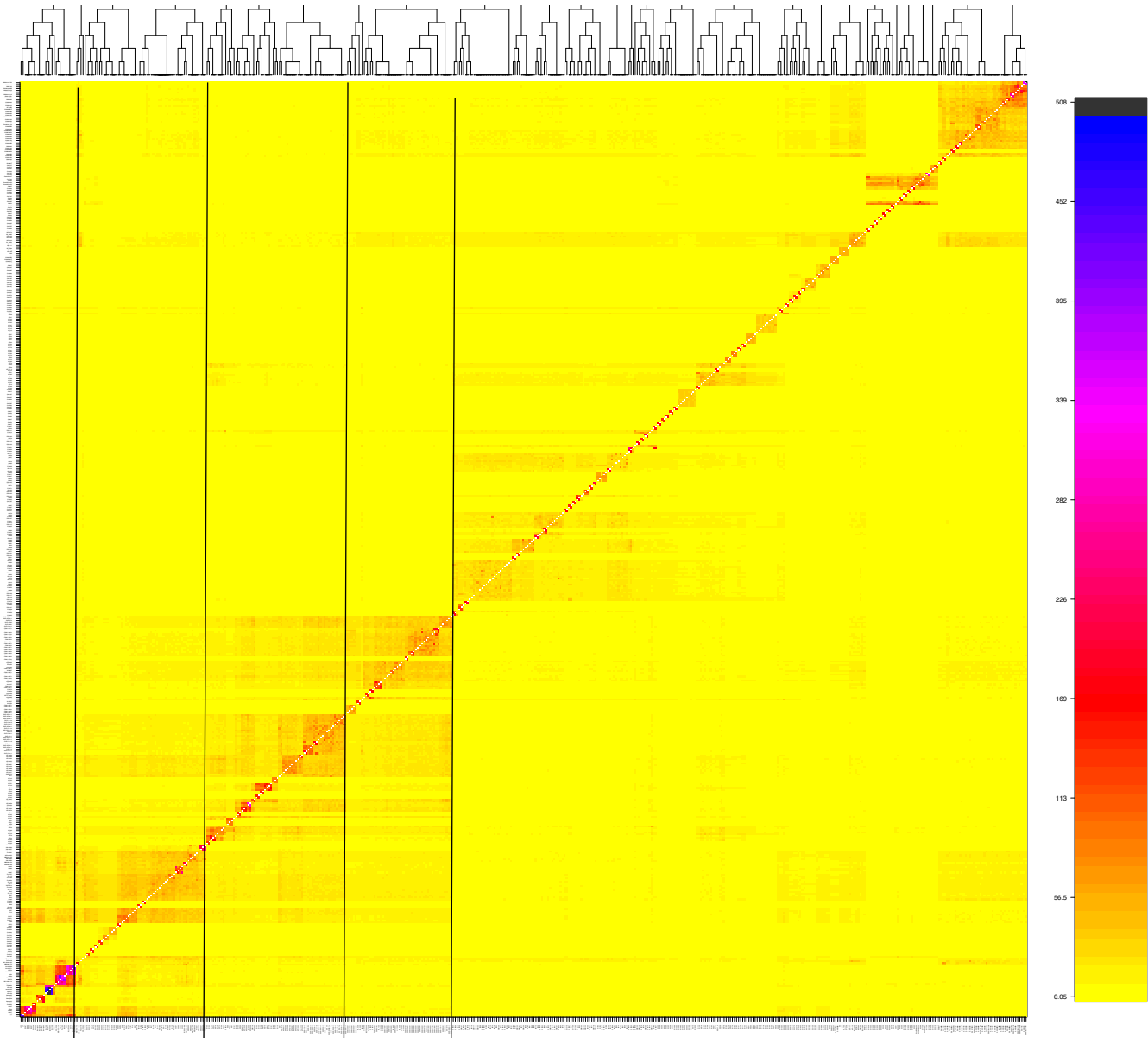
- Characterizing and mapping the population structure of *H. pylori* across Africa using an expanded dataset incorporating both public and unpublished genomic sequences
- Exploring the potential impact of the genetic diversity and population structure on the pathogenicity and the clinical relevance of *H. pylori* isolates colonizing Africa
- Characterizing key virulence factors of *H. pylori* across Africa
- Discussing the *H. pylori* related gastric disease risk at the continent level

Methods



- New *H. pylori* genomes collected between 2018 – 2023 were sequenced using various platforms (i.e., MiSeq, Oxford Nanopore, HiSeq, and PacBio)
- Published *H. pylori* genomes retrieved from NCBI and my lab. data.
- Population clustering using fineSTRUCTURE, DAPC, and ML phylogenetic at both the pangenome and MLST levels
- Screening of the virulome using ABRICATE against a customized database (i.e., HpVDB) with 200 species specific genes

H. pylori population genetics in Africa: inferences from an expanded dataset

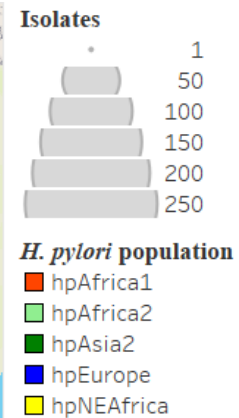
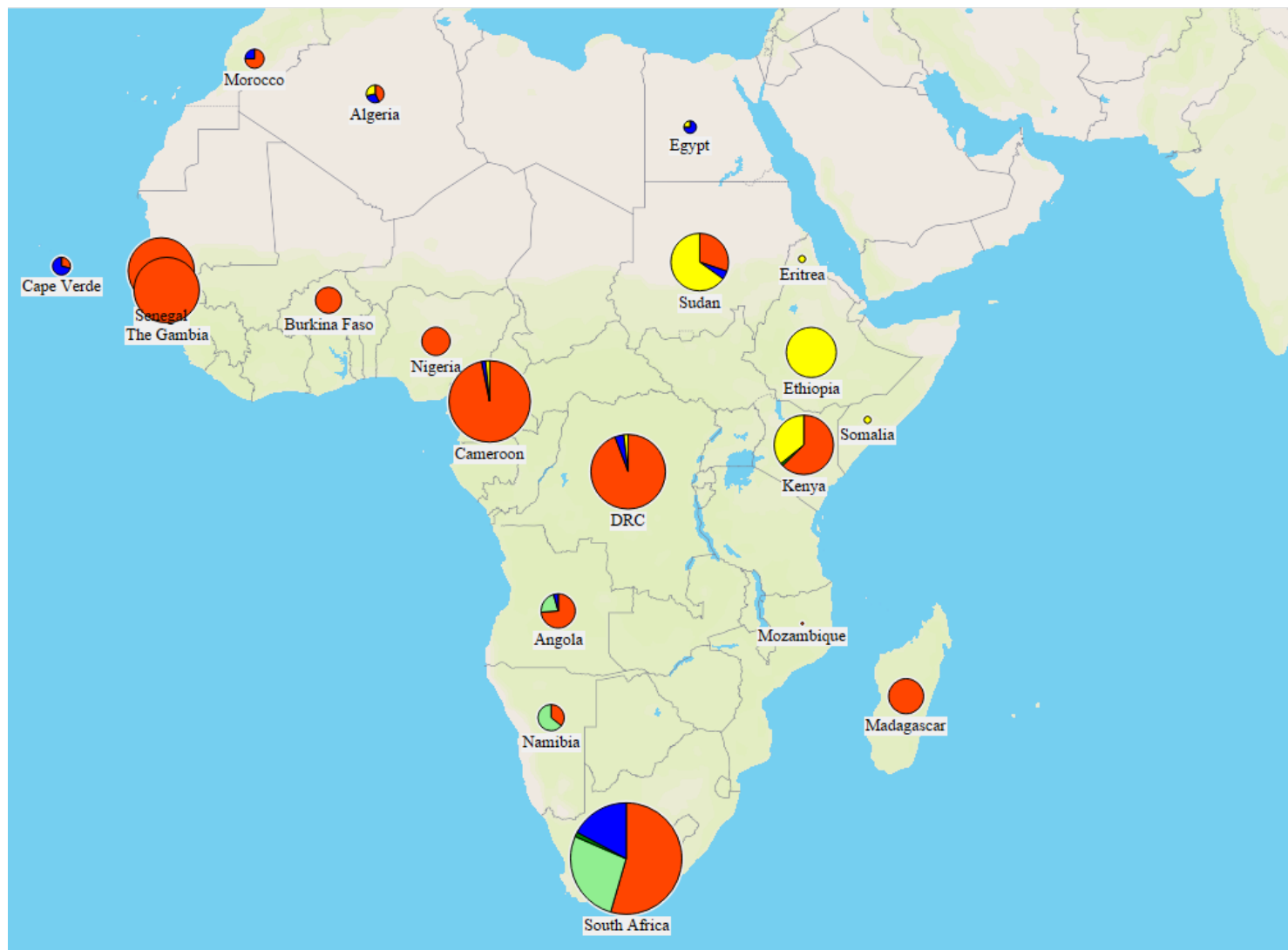


Cumulated population Genetics of *H. pylori* Across the African Continent

(~ 1000 MLST sequences from pubMLST and Yamaoka Lab)

***H. pylori* population genetics and ancestry through the African continent (fineSTRUCTURE; n=387)**

Geographical distribution of *H. pylori* population genetics across African countries



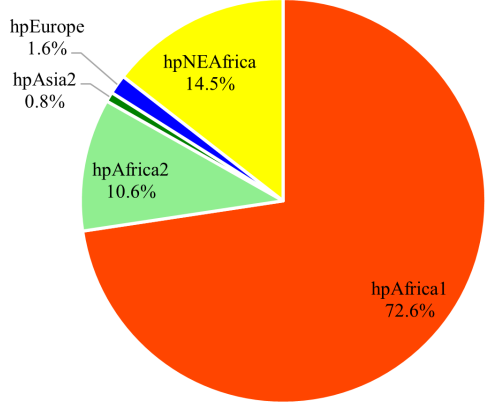
Country	n	%
1 Algeria	7	0.8
2 Angola	23	2.5
3 Burkina Faso	14	1.5
4 Cameroon	125	13.5
5 Cape Verde	7	0.8
6 Congo*	105	11.3
7 Egypt	4	0.4
8 Eritrea	2	0.2
9 Ethiopia	48	5.2
10 Kenya*	67	7.2
11 Madagascar	24	2.6
12 Morocco	8	0.9
13 Mozambique	1	0.1
14 Namibia	14	1.5
15 Nigeria**	16	1.7
16 Senegal	83	9.0
17 Somalia	2	0.2
18 South Africa	233	25.1
19 Sudan	63	6.8
20 The Gambia	81	8.7

Geographic distribution of *H. pylori* population genetics through the African continent

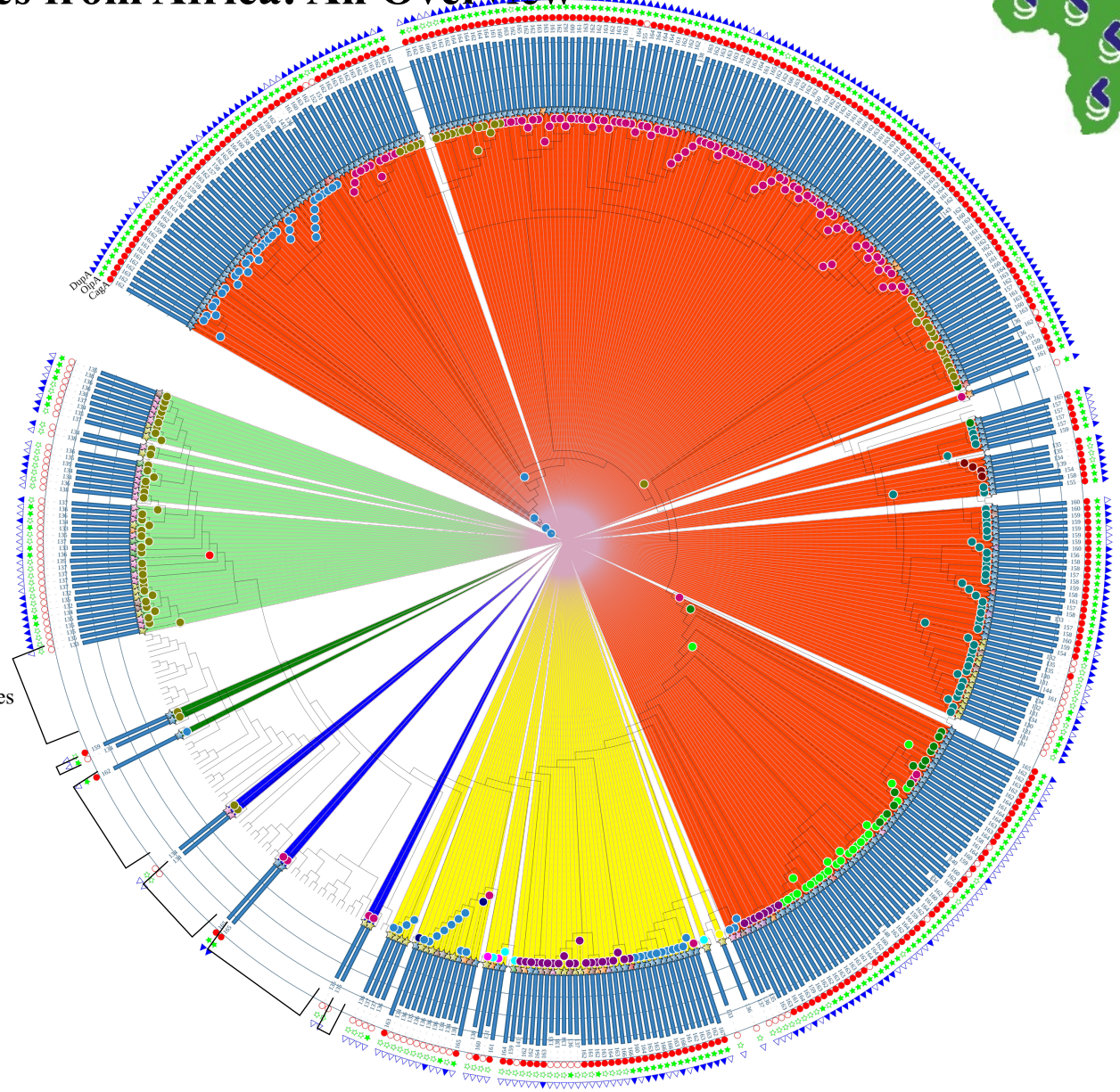
(~ 1000 MLST sequences from pubMLST and Yamaoka Lab)

Distribution of Virulence Factors in *H. pylori* Genomes from Africa: An Overview

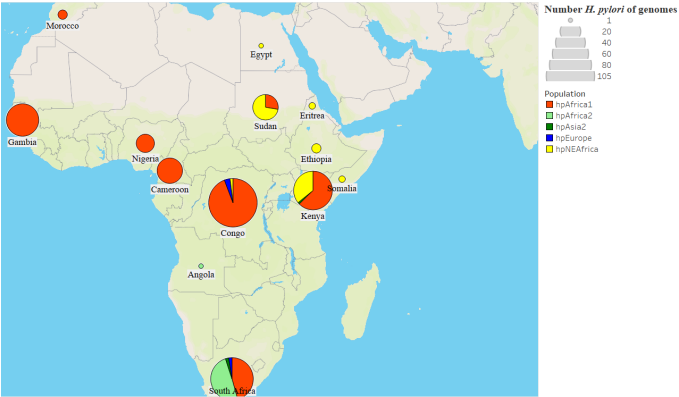
(387 genome sequences from NCBI and Yamaoka Lab)



H. pylori population		Country
hpAfrica1	Orange	Angola
hpNEAfrica	Yellow	Cameroon
hpEurope	Blue	DRC
hpAfrica2	Light Green	Egypt
hpAsia2	Dark Green	Eritrea
VacA type		Ethiopia
s1m1i1d1	Blue Star	Kenya
s1m1i1d2	Orange Star	Morocco
s1m1i2d2	Green Star	Nigeria
s1m2i1d1	Red Star	Somalia
s1m2i1d2	Purple Star	South Africa
s1m2i2d2	Brown Star	Sudan
s2m1i2d2	Pink Star	The Gambia
s2m2i1d2	Grey Star	
s2m2i2d2	Yellow Star	
VFs found		
	Dark Blue	



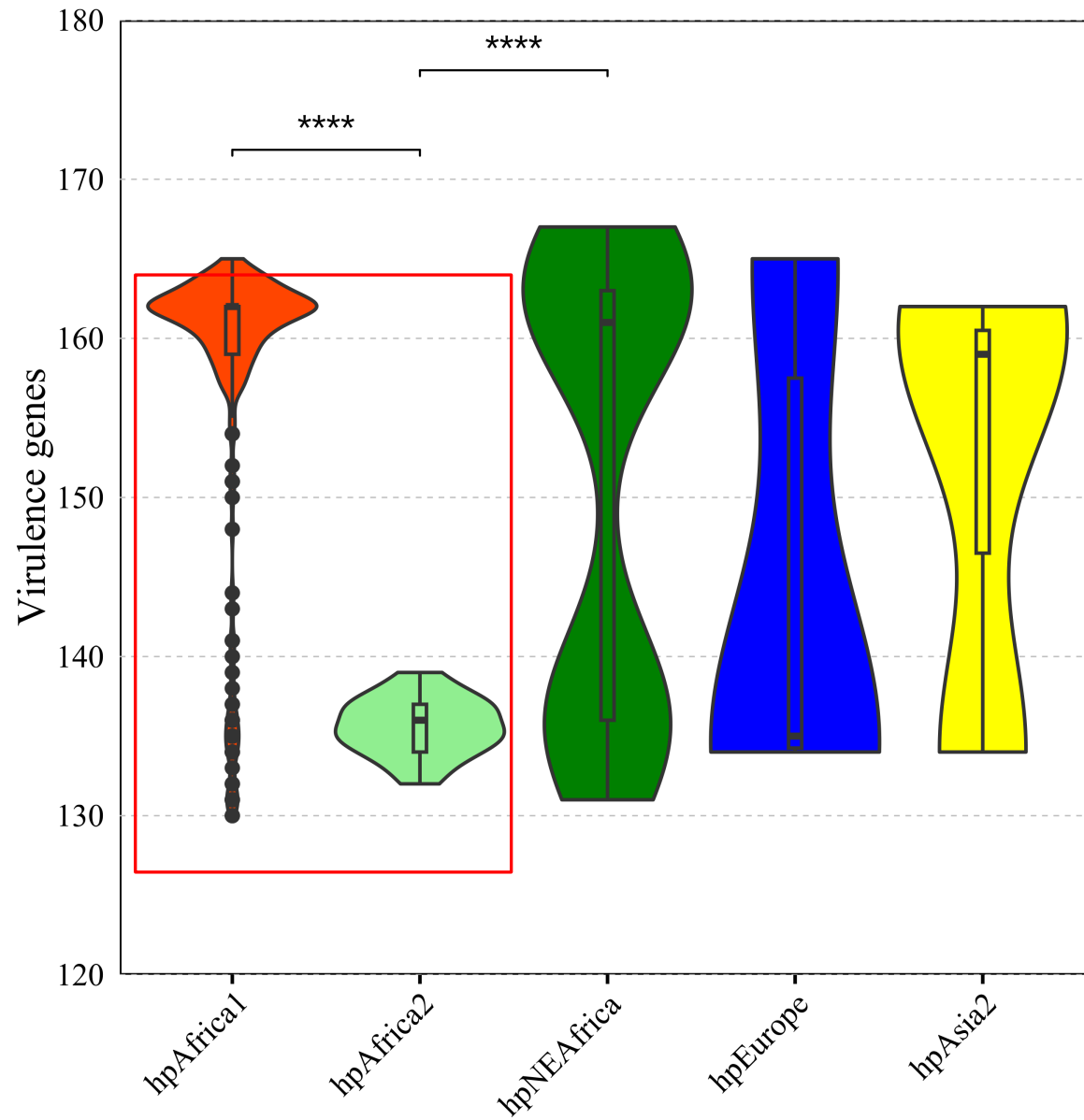
Population genetics of *H. pylori* genomes (n=387)



Origin countries of *H. pylori* genomes (n=387)

Non-African reference genomes

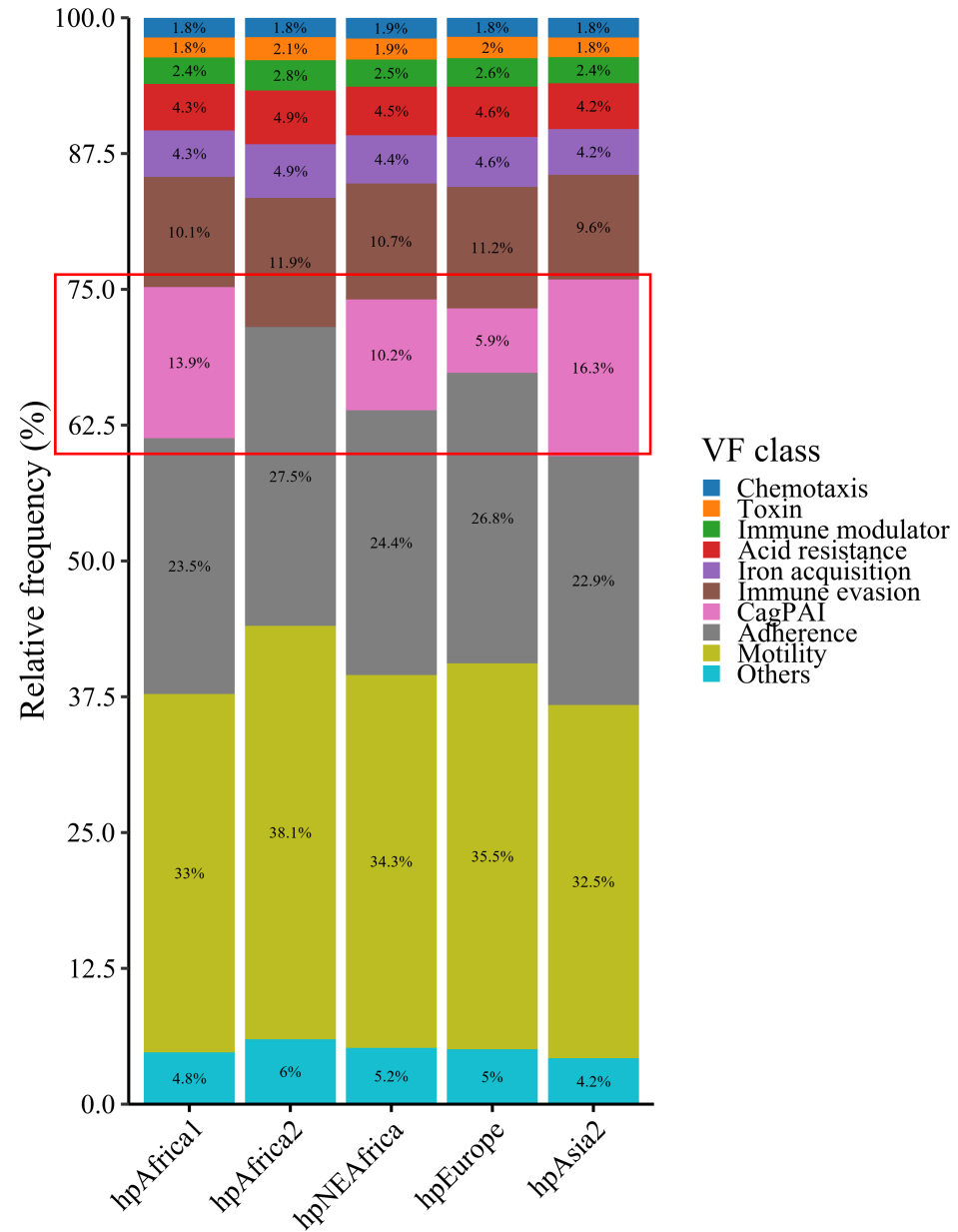
Phylogeographic Distribution of key *H. pylori* Virulence Factors Across Africa



DISTRIBUTION OF *H. PYLORI* VIRULENCE GENES ENCODED AMONG AFRICAN POPULATION

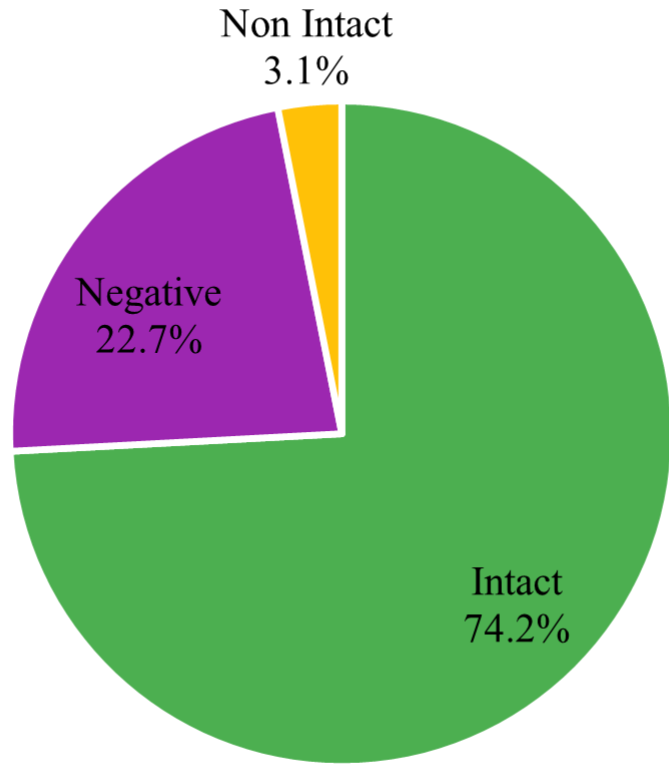


Distribution of *H. pylori* virulence factors across Africa

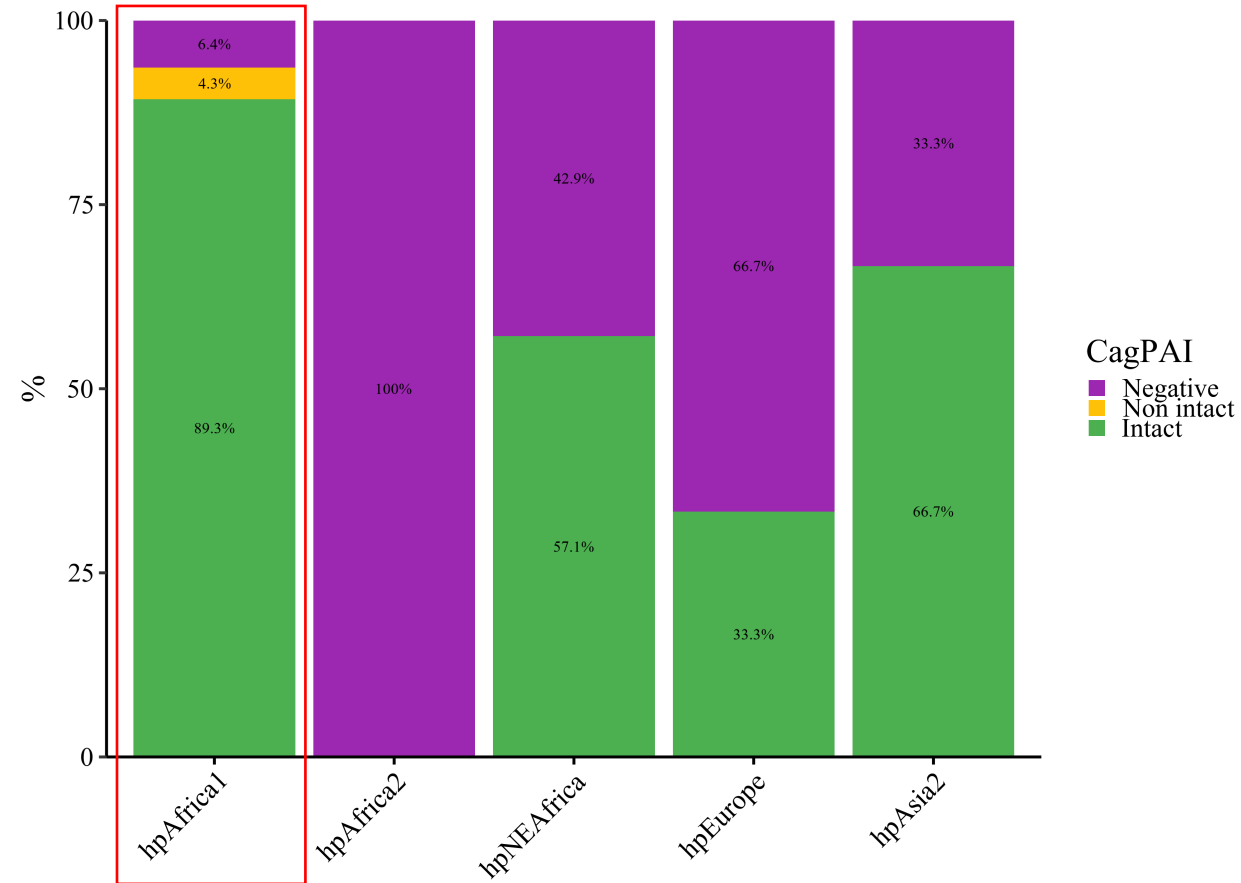


Distribution of different classes of Virulence Factors within *H. pylori* Genomes from Africa

Distribution of the *H. pylori* *cag* PAI across Africa and its population genetics

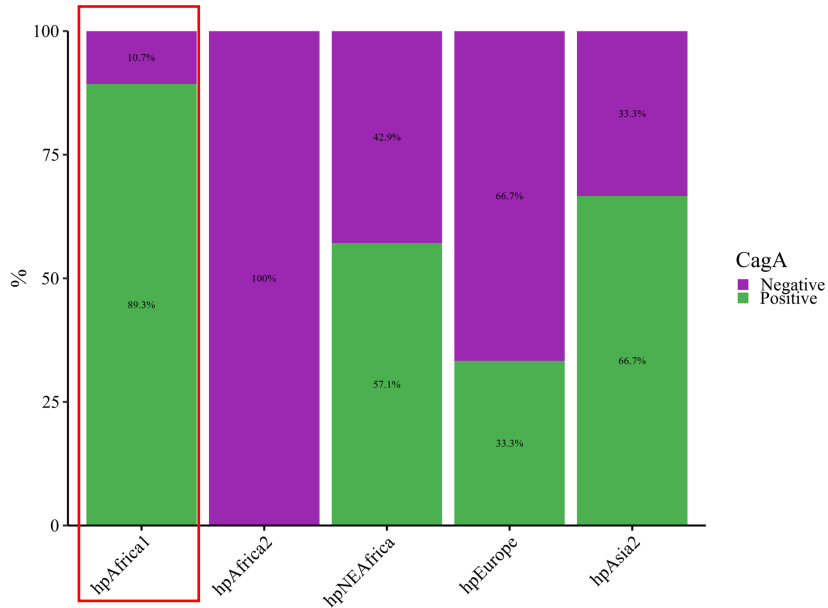
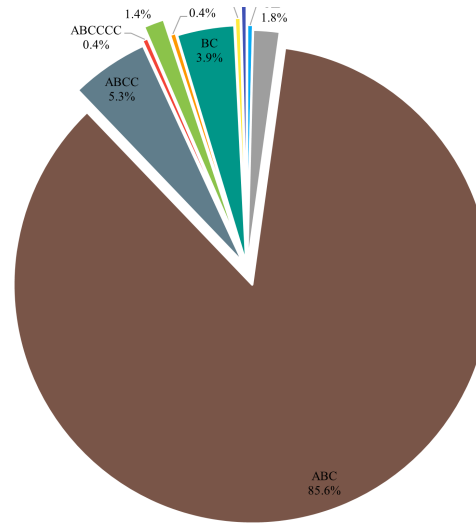
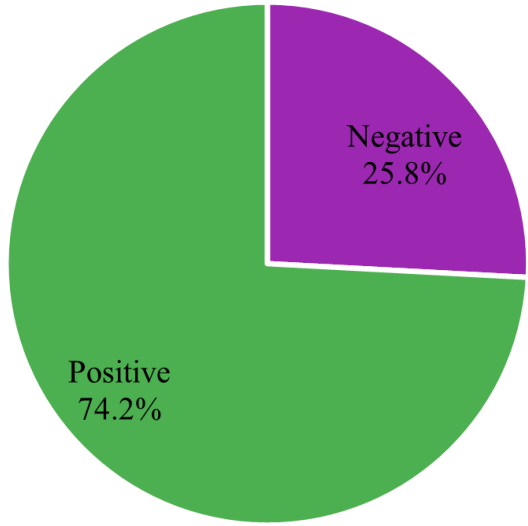


H. pylori *cag* PAI structure across Africa

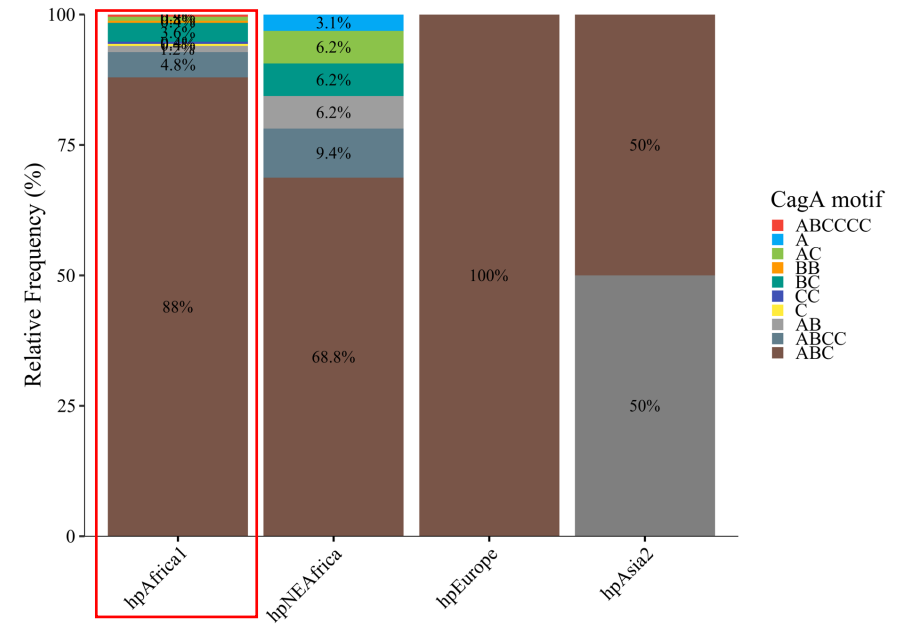


H. pylori *cag* PAI across African population genetics

Distribution and typing of the *H. pylori cagA* gene across Africa and its population genetics



H. pylori cagA across African population genetics



H. pylori cagA types across African population genetics

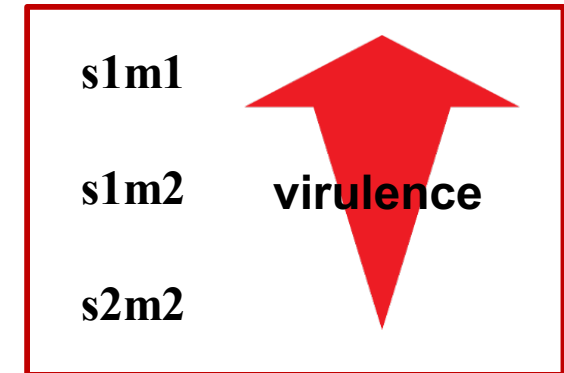


VacA

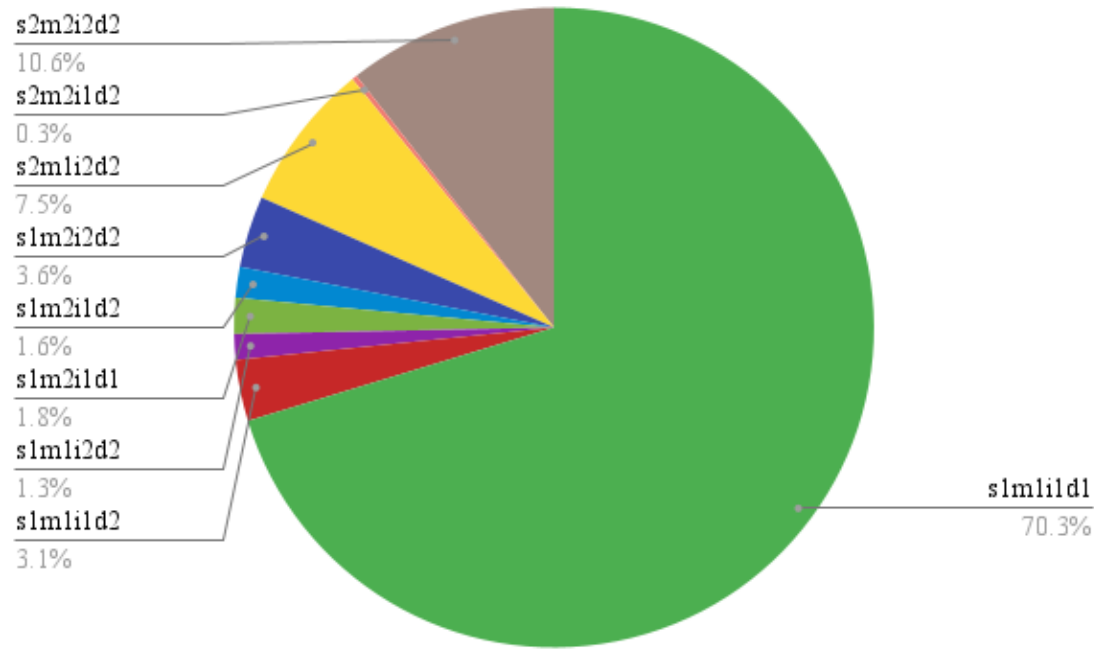
vacA s1/i1/d1/m1



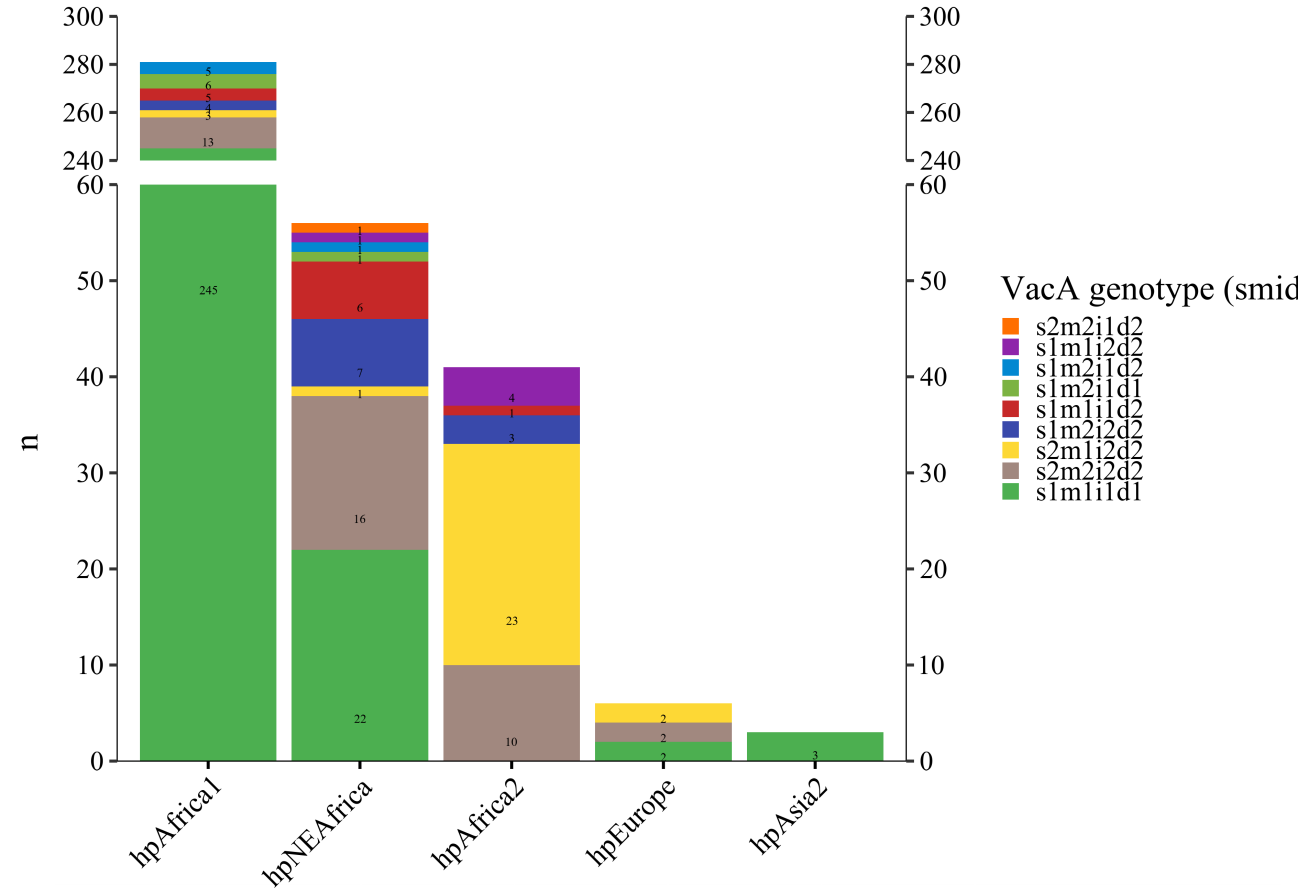
vacA s2/i2/d2/m2



Typing of *H. pylori* Vacuolating Cytotoxin Antigen A (VacA) across Africa



Distribution of *H. pylori* VacA types across Africa



Distribution of *H. pylori* VacA types across African population genetics

Conclusion



- Unlike others, *hpAfrica1* isolates mostly exhibited a complete *cag* PAI, featuring a CagA oncoprotein with Western ABC-type EPIYA patterns, a *s1m1i1d1*-type VacA, as well as 'ON'-type OipA and type 1 HopQ OMPs.
- In contrast, *hpAfrica2* and *hpEurope* isolates did not encode both the *cag*PAI region and the *cagA* gene while *hpNEAfrica* isolated exhibited a mixed virulence profile
- The species' population structure shapes the virulence of *H. pylori* in Africa with *hpAfrica1*, the most extended and most virulent African population.
- These insights are pivotal for understanding the interplay between *H. pylori* genetic diversity and its pathogenicity, thereby informing targeted therapeutic strategies tailored to specific population subgroups.



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