Helicobacter pylori : The existence of the African enigma

African Helicobacter & Microbiota Study Group

Inaugural AHMSG Conference

Mashiko Setshedi 17 Aug 2024

University of Cape Town • iDyunivesithi yaseKapa • Universiteit van Koapstad •

The African enigma

Gut, 1992, **33**, 429–431

Gut

Leading article

Helicobacter pylori: the African enigma

Data on *Helicobacter pylori* infection in Africa are at odds in several aspects with those published in the west. Gastric *H pylori* infection is common, almost ubiquitous in Africa, but the pattern of infection, age of acquisition, environmental, dietary, and genetic influences are different from those in the west. These differences alter the pathological role and clinical relevance of the organism in Africa where, apart from gastritis, there is no established correlation between *H pylori* infection and upper gastrointestinal disease.

Epidemiology

The measurement of circulating antibodies to *H pylori* using an enzyme linked immunosorbant assay provides a simple, reliable, and non-invasive means of diagnosing *H pylori* infection, with a sensitivity of 95% and specificity of 85%.[1]

reviewed by Tovey and Tunstall,[15] who defined areas of high incidence (Nile/Congo watershed and coastal region of West Africa) and low incidence (northern savannah of West Africa). These differences in incidence are not paralleled by differences in the prevalence of *H pylori* infection.

In the dry savannah of northern Nigeria, duodenal ulcer is uncommon. This was first noted by Tovey and Tunstall,[15] and recently confirmed.[16] In a random community survey 28% of adults had experienced dyspepsia in the preceding six months,[16] a figure remarkably similar to the 25–38% recorded in the UK.[17–19] Using the same definition of dyspepsia, and in the same population, duodenal ulcer was found in only 18 of 162 patients, who underwent endoscopy for their dyspepsia[20] – a prevalence of 111/1000 patients with dyspepsia, compared with 178–305/1000 in the UK.[17–19] Duodenal ulceration is then less common in northern Nigeria than in the UK

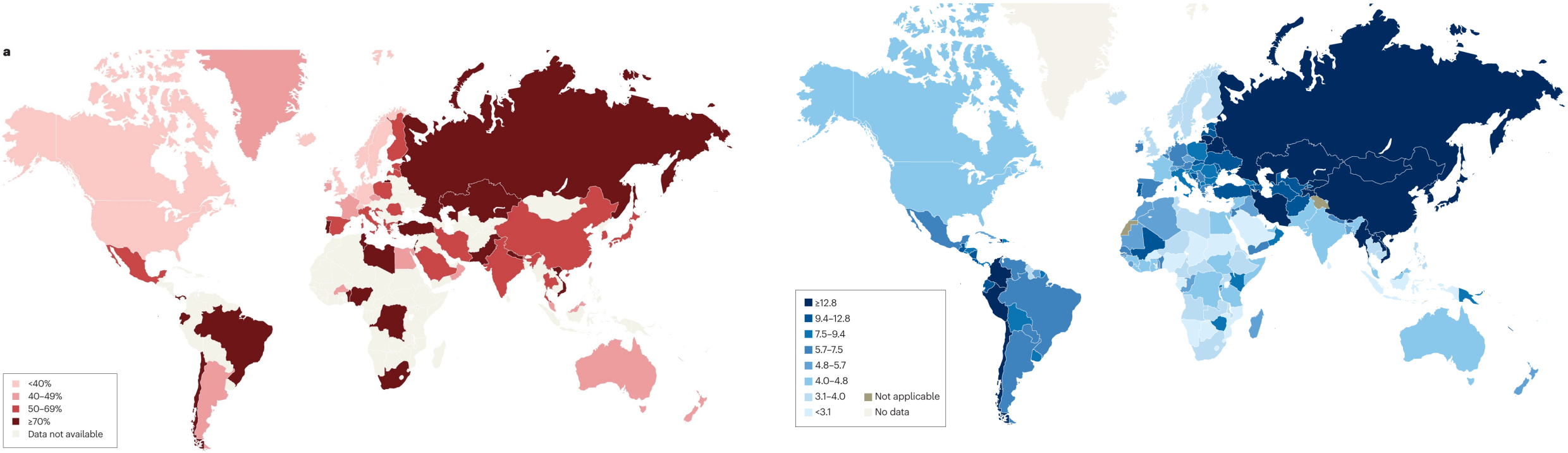
- Gastritis is common (80-100% of patients), GC in some regions of Africa is only ~2-3%
- Low rates may be due to:
  - acquisition of infection in childhood, which confers a less pathogenic inflammatory phenotype
  - low rate of intestinal metaplasia
  - protective environmental factors such as low rates of smoking and a nutritious diet of vegetables in Africa

Holcombe C. Gut 1992.33:429-43142.

Does the data support the enigma?

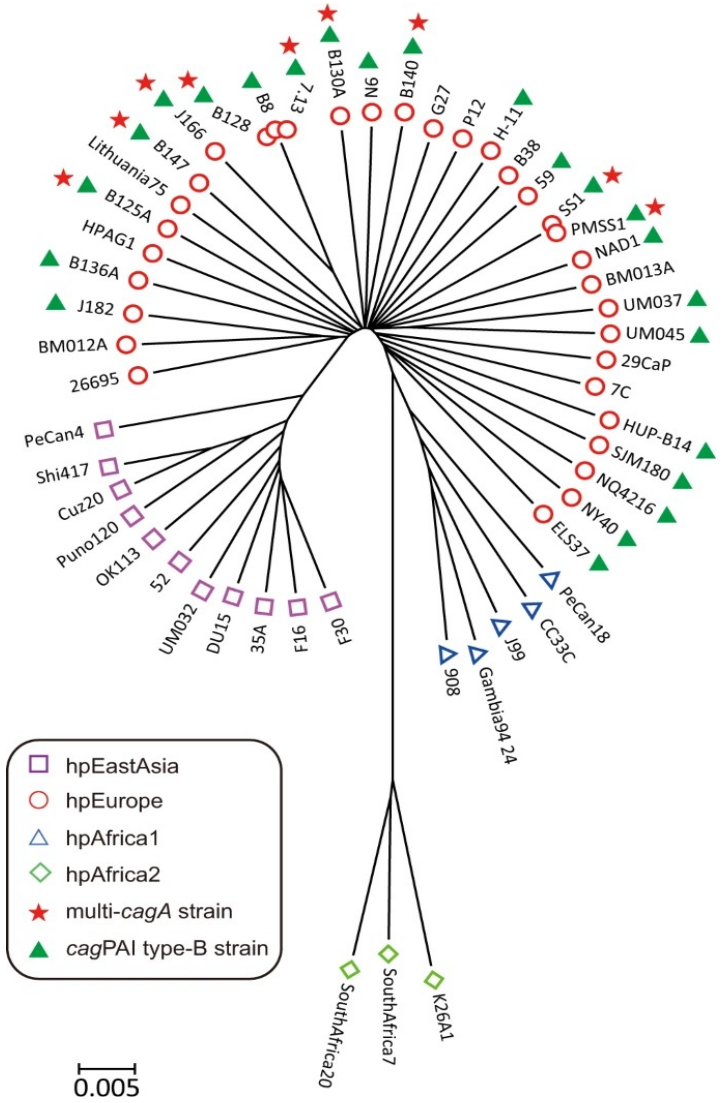
1. Epidemiological data
2. African *H. pylori* strains
3. Co-infection with other pathogens
4. Co-evolution theories
5. Other factors

H. pylori prevalence vs GCA incidence - dissociation



Malfertheiner P, et al. 2023. Nature Reviews Disease Primers;9:19.
Thrift, PA et al. 2023. Nature Reviews Clinical Oncology;20:338-349.

Pathogenicity of *H. pylori* strains



- Prevalent *H. pylori* strains in Africa (particularly hpAfrica1 & hpAfrica2)[1, 2]
- hpAfrica2 may be less oncogenic[3]
- Genetic diversity and evolutionary patterns of *H. pylori* (genomic differentiation between different strains, especially those from East Asia)[4]

1. *Li Y, et al. Lancet Gastroenterol Hepatol 2023.8;6:553–64.*
2. *Palamides P, et al. Sci Rep 2020.10;1:11409.*
3. *Graham DY, et al. J Dig Dis 2009.10;2:77–84.*
4. *Thorell K, et al. PLoS Genet 2017.13:2.*
5. *Su H, et al. Sci Rep 2019.9:11203.*

Co-infection with parasites

- Host factors & high burden of parasitic infections may bias the inflammatory cytokine response to a Th2 type[1]

Animal studies

- co-infection with **nematodes** in mice with *H. pylori* **protects against gastric atrophy** mediated by downregulation of TNF-α and IL1-β, and upregulation of IL-4 and IL-10[2]

- in *H. pylori* infected transgenic mice, co-infection with **helminths** resulted in **reduced gastric atrophy** ($p<0.04$) and **dysplasia** ($p<0.02$)[3]

1. *Ghoshal UC, et al. Indian J Gastroenterol 2010. 29;3:95-100.*
2. *Fox JG, et al. Nat Med 2000. 6;5:536-42.*
3. *Whary MT, et al. Microbes Infect 2014. 16;4:345-55.*

Co-infection with parasites

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Human studies

- in a study from Colombia (**a high endemic area for parasites**), with virulence-associated genotypes of *H. pylori*, the rate of **gastric cancer** was **low**[2]

- in another study from China, co-infection with **helminths** altered serological IgG responses as well as the pepsinogen I/II ratio, with attendant **lower risk of gastric atrophy**[3]

- co-infection with *H. pylori* and **intestinal helminths** was associated with increased IL-4 expression, together with **lower degrees of inflammation and gastric atrophy**, compared to mono-infected patients (Venezuela)[4]

1. *Bravo LE, et al. Am J Gastroenterol 2002. 97;11:2839-42.*
2. *Du Y, et al. Microbes Infect 2006. 8;1:52-60.*
3. *Fuenmayor-Boscán A, et al. Indian J Gastroenterol 2020. 39;2:186-195.*

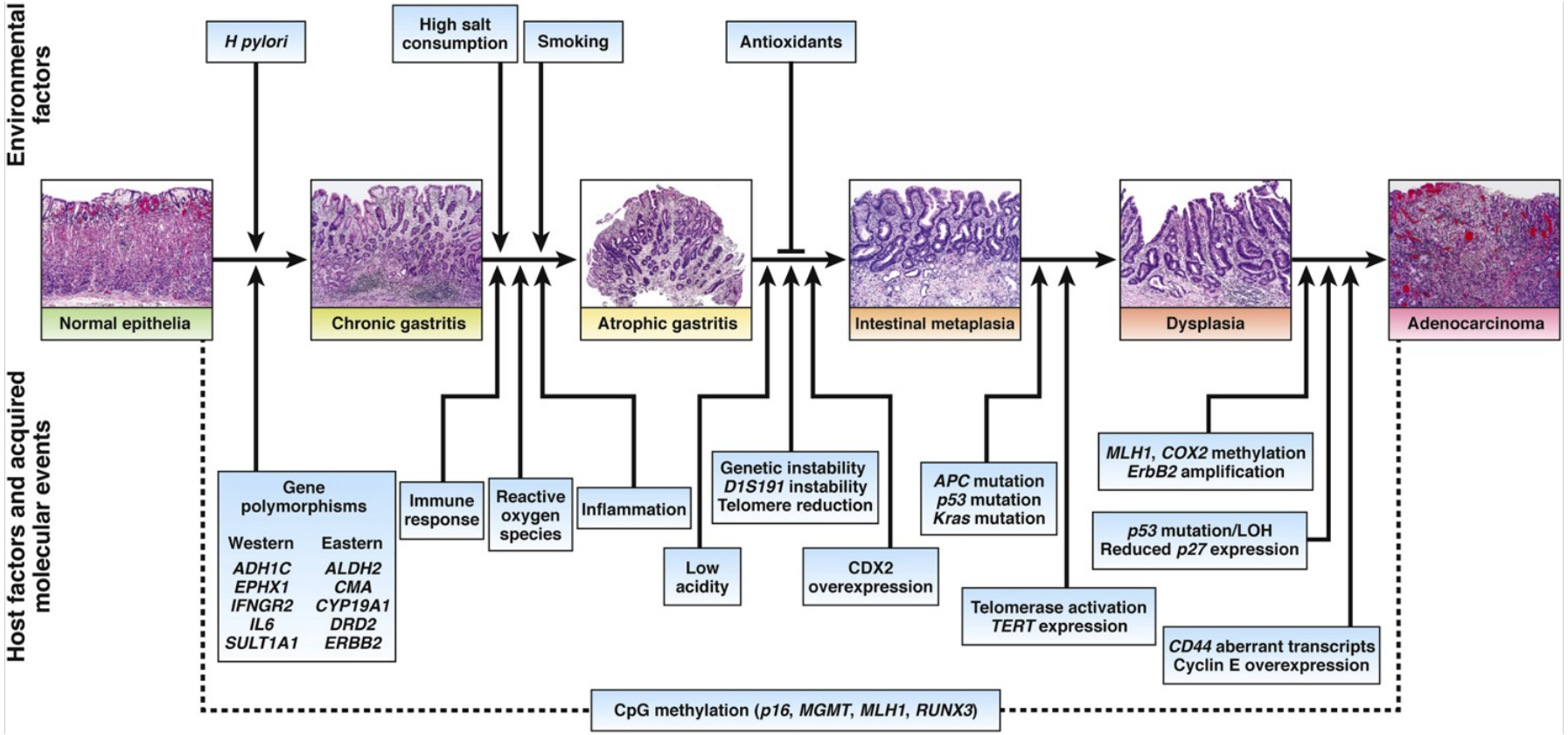
Co-evolution hypothesis

- Humans and *H. pylori* co-evolved to reciprocally impact each other; the risk of GCA is higher in host-pathogen genomic pairs that did not co-evolve[1]
- Those with African **ancestry** demonstrate co-evolution with *H. pylori* compared to their European/Asian counterparts, in whom this appears to be maladapted[2]
- Host response to *H. pylori* infection was greatly shaped by the human ancestry, with variability on innate immune system and metabolism[2]

Photo by Minden Pictures/Superstock

1. *Kodaman, N et al. Proc Natl Acad Sci USA 2014.111;4:1455-60.*
2. *Cavadas B, et al. Microorganisms, 2021.9:2.*
3. *https://allyouneedisbiology.wordpress.com/2015/10/18/evolution-coevolution/*

Arguments against the enigma: pre-cancerous lesions



1. Correa P, et al. Lancet, 1975. 2;7924:58-60.
2. Correa P. Cancer Res, 1988. 48;13:3554-60.

Arguments against the enigma: pre-cancerous lesions

- Prevalence of IM is 17 % in Zambia vs 13.8 % in Turkey, 12-13.7 % in American cohorts respectively providing further evidence against the African enigma[1, 2, 3]

- A decrease in GCA risk is seen in migrant populations from high risk regions who move to low risk regions[4]

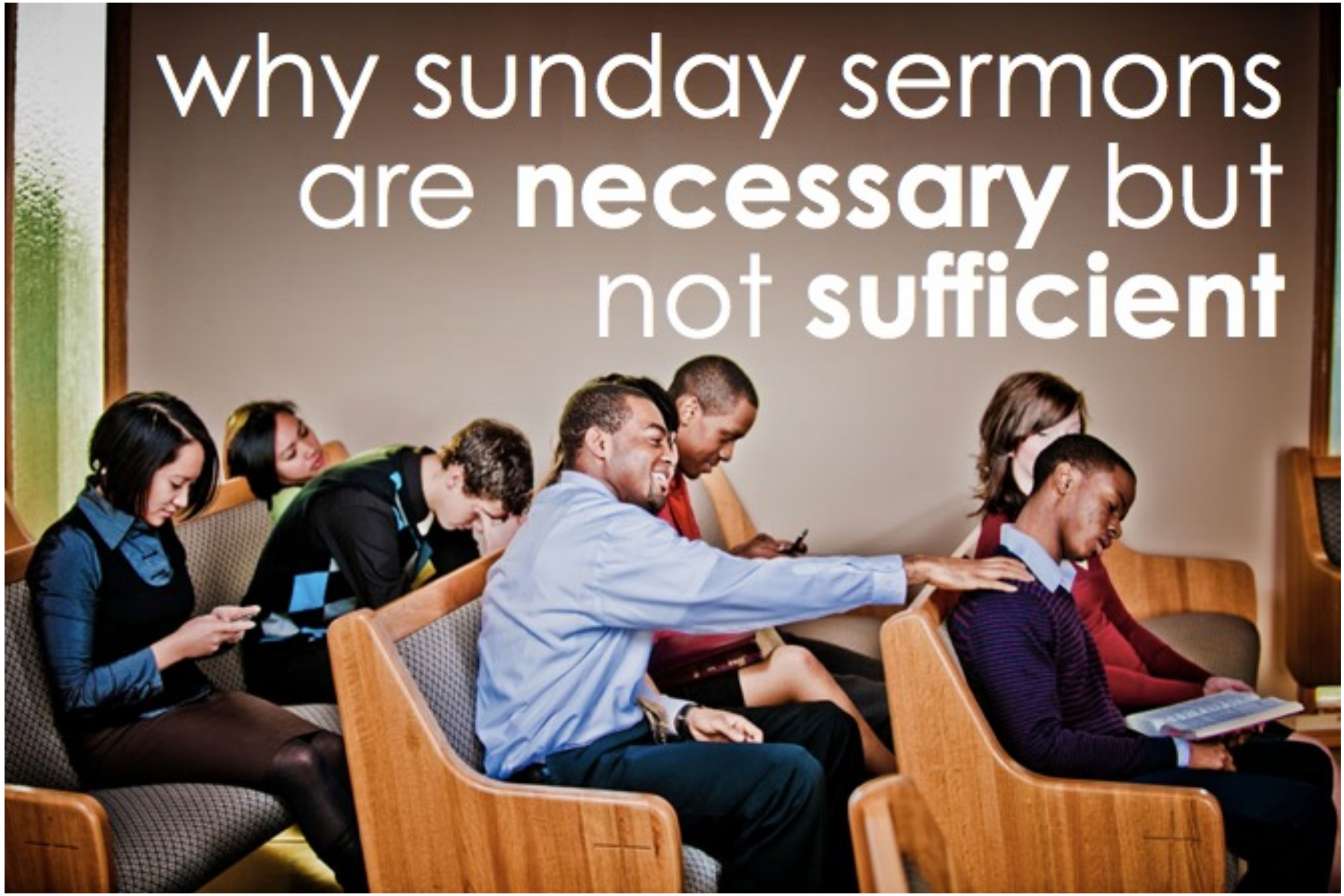
1. *Kayamba V, et al. S Afr Med J 2013.103:255-9.*
2. *Olmez S, et al. Gastroenterology Research and Practice 2015.434039.*
3. *Nguyen TH, et al. Clin Gastroenterol Hepatol 2021.19: 269-76.*

Arguments against – virulence factors

- Data shows that virulence factors are similar as elsewhere[1]

- Two studies from Zambia showed that Cag A and Vac A were associated with acute gastritis but not gastric cancer or premalignant lesions[2, 3]

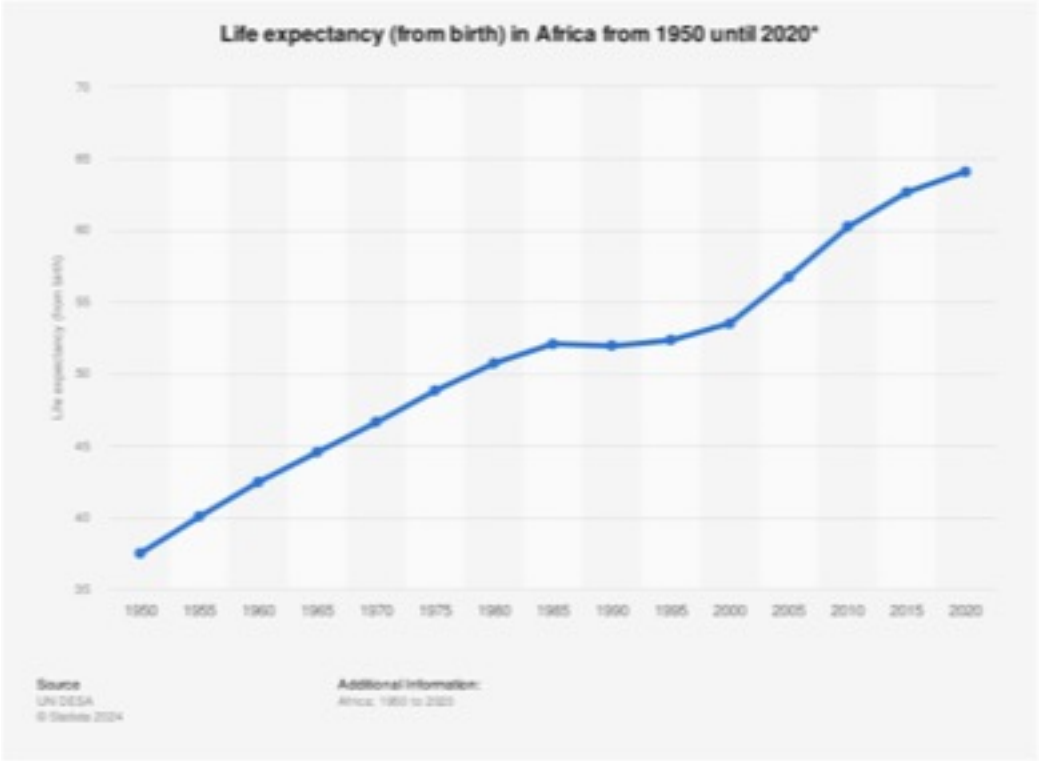
1. *Breurec S, et al. Clin Microbiol Infect. 2012 Feb;18(2):153-9.*
2. *Louw JA, et al. Helicobacter 2001.6:268-73.*
3. *Palamides P, et al. Sci Rep 2020.10;020:66128.*


why sunday sermons
are **necessary** but
not **sufficient**

Other arguments against

- Graham DY, et al[1]:
  - **GC would be expected in regions with longer life expectancy and higher rates of atrophic gastritis**
  - low rates of GC may reflect selection bias of studies that include populations with limited access to endoscopy and limited data

"The enigma is not based on experimental data therefore it is a myth!
Rather than focus on individual populations, it is the bacterium, host and environmental factors that play a role in disease expression."



1. *Graham D Y, et al. J Dig Dis, 2009. 10:77-84.*
2. *https://www.statista.com/statistics/1076271/life-expectancy-africa-historical/*

Further arguments against

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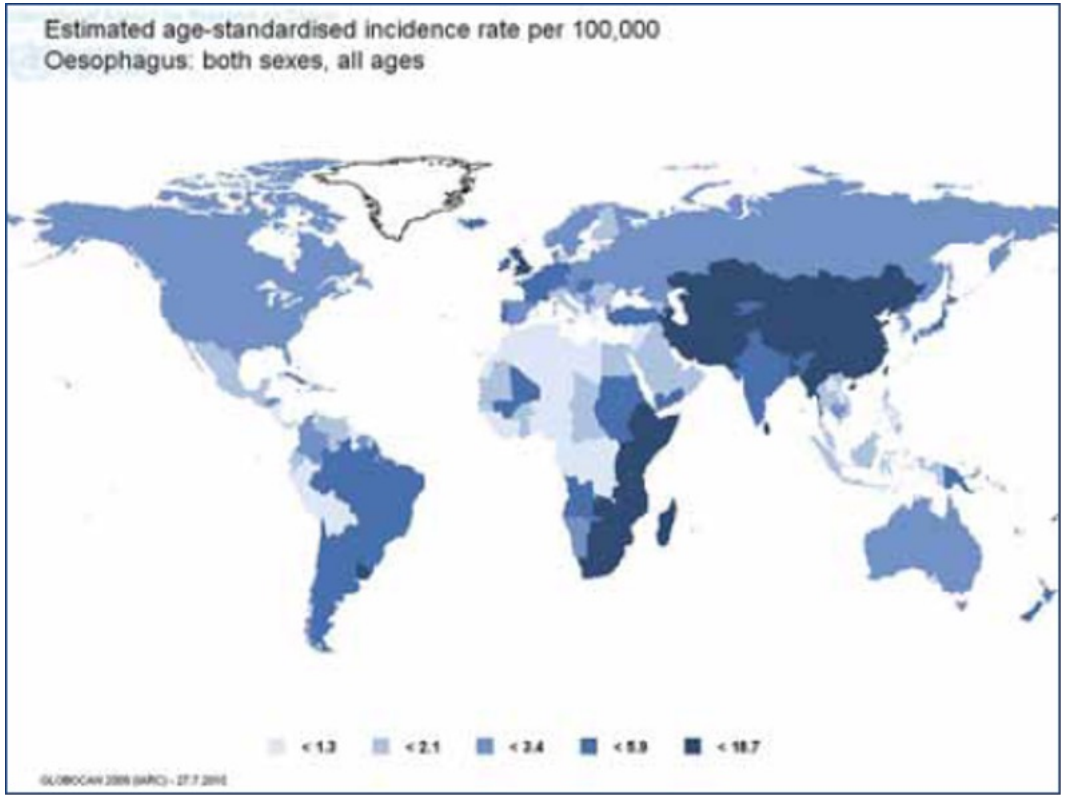

1. Graham D Y, et al. J Dig Dis, 2009. 10:77-84.
2. Mazidimoradi A, et al. Thorac Cancer 2023.14:2408-2458.
3. Gona P, et al. Obes Sci Pract 2024.10: e715.
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Very high incidence of oesophageal cancer throughout Africa[2,3]
Accepted data on oesophageal cancer (not questioned), use the same diagnostic tool?
The same should apply for GCA.
This argument no longer valid!

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1. *Graham D Y, et al. J Dig Dis, 2009. 10:77-84.*
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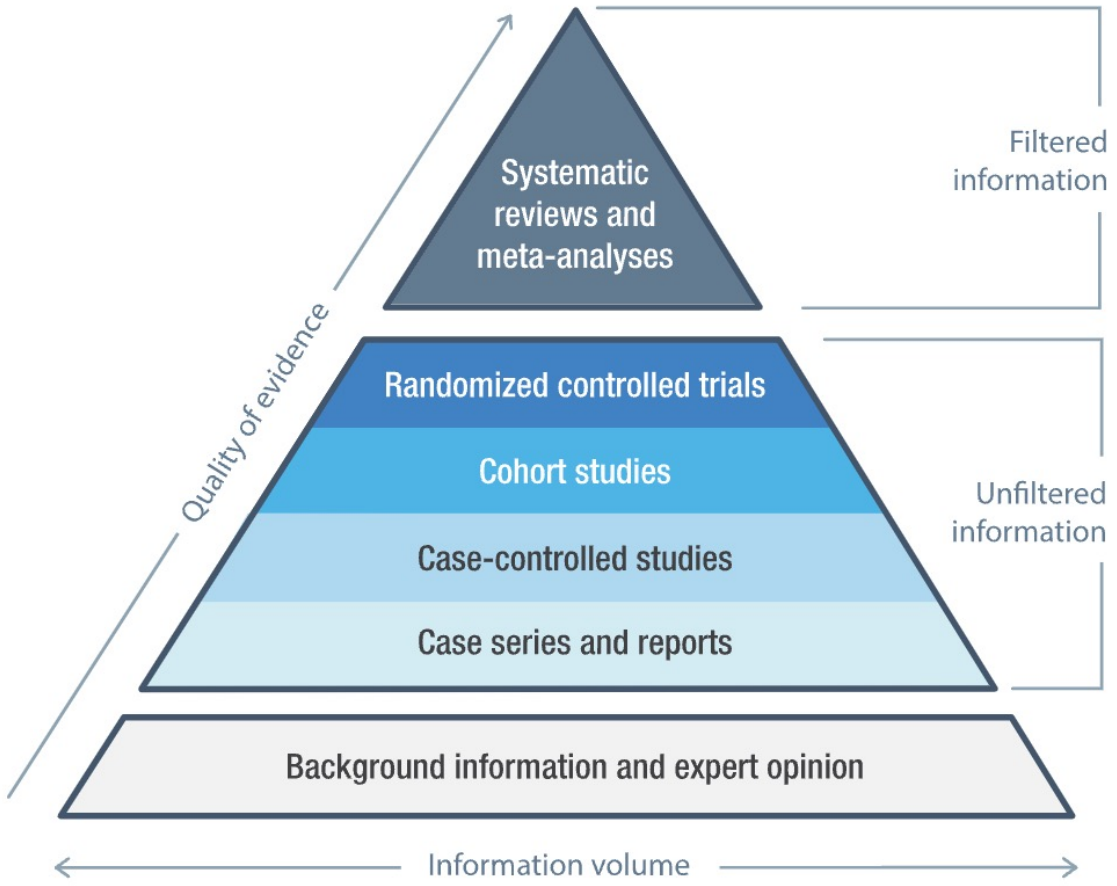
Recent GCA data in Africa



ecancermedicalscience

Gastric cancer in Sub-Saharan Africa – a systematic review of primary data

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[2]University of California San Francisco, San Francisco, CA, USA
[3]National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa
[4]Stellenbosch University, Faculty of Medicine and Health Sciences, Cape Town, South Africa
[5]University of California Davis, Davis, CA, USA

Abstract

Introduction: Gastric cancer (GC) is the third leading cause of global cancer-related mortality. Despite the shifting burden of GC to low-and middle-income countries, the data regarding incidence, treatment, and outcomes in these settings are sparse. The primary aim of this systematic review was to aggregate all available data on GC in sub-Saharan Africa (SSA) to describe the variability in incidence across the region.

Methods: Studies reporting population-based primary data on GC in SSA were considered. The inclusion was limited to primary studies published between January 1995 and March 2022 which comprised of adult patients in SSA with GC. Studies without accessible full text in either French or English language were excluded. Unadjusted GC incidence rates with their standard errors for each study were recalculated from the crude numerators and denominators provided in individual studies.

Results: A total of 5,626 articles were identified in the initial search, of which, 69 studies were retained. Reported incidence rates ranged from a high of 5.56 GC cases per 100,000 in Greater Meru Kenya to a low of 0.04 GC cases per 100,000 people in Benin City Nigeria. The overall crude pooled incidence was 1.20 GC cases per 100, 000 (95%CI 1.15–1.26) with a variability of 99.83% (I^2 p < 0.001). From the 29 high-quality population-based registry studies the crude pooled incidence was 1.71 GC cases per 100,000 people (95%CI 1.56–21.88) with a variability of 99.60%.

Conclusion: This systemic review demonstrates that GC incidence is highly variable across SSA. The limited data on GC treatment, mortality, and survival presents a significant challenge to providing a complete epidemiologic description of the burden of GC in SSA. There is a need for further robust data collection, exploration, and research studies

Review

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Crude pooled incidence was 1.71 GC cases per 100,000

Ramadhar A, et al. Ecancermedicalscience 2024.18:1680.
https://openmd.com/guide/levels-of-evidence

There's none so blind as they that won't see.

~ Jonathan Swift

The way forward

- Graham DY, et al:
  - it is not uncommon for infectious diseases to present with variable clinical expressions in different regions
  - GC would be expected in regions with longer life expectancy and higher rates of atrophic gastritis
  - low rates of GC may reflect selection bias of studies that include populations with limited access to endoscopy and limited data

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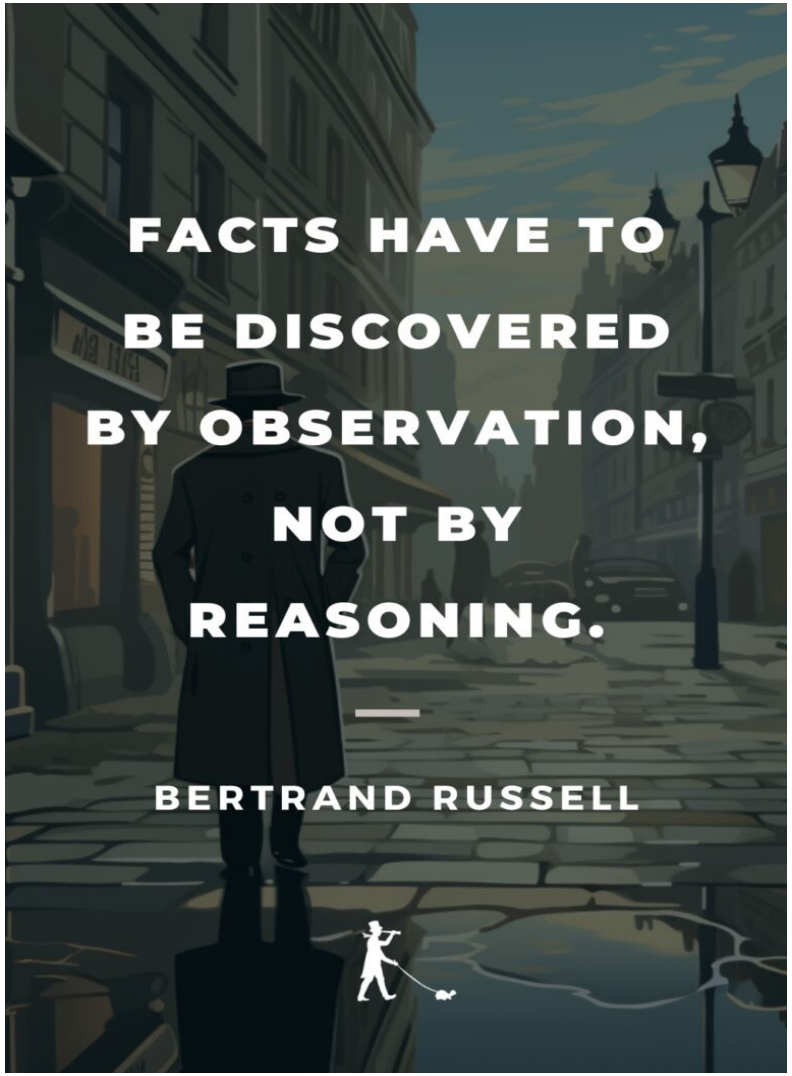
In the dry savannah of northern Nigeria, duodenal ulcer is uncommon. This was first noted by Tovey and Tunstall,[15] and recently confirmed.[16] In a random community survey 28% of adults had experienced dyspepsia in the preceding six months,[16] a figure remarkably similar to the 25–38% recorded in the UK.[17–19] Using the same definition of dyspepsia, and in the same population, duodenal ulcer was found in only 18 of 162 patients, who underwent endoscopy for their dyspepsia[20] – a prevalence of 111/1000 patients with dyspepsia, compared with 178–305/1000 in the UK.[17–19] Duodenal ulceration is then less common in northern Nigeria than in the UK

The African enigma exists. Full stop.



100 000 years of *H. pylori* in Africa but rates of GCA over time have still not changed.

Ke a leboga!