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The impact of *Helicobacter pylori* and intestinal helminth infections on gastric adenocarcinoma and inflammatory bowel disease in Sub-Saharan Africa

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Gastric adenocarcinoma (GCA) is the 5th leading cancer globally with an estimated 1.1 million cases reported in 2020. Ninety percent of non-cardia GCAs are attributable to *Helicobacter pylori* (*H. pylori*), the most prevalent bacterial infection globally. Rates of *H. pylori* infection are highest in Sub-Saharan Africa (SSA), yet surprisingly low numbers of GCAs are reported in the region. A similar phenomenon is seen with the inflammatory bowel diseases (IBD), Crohn's disease, and ulcerative colitis. These disorders have risen dramatically over the past century in high income countries across the globe, with sharp increases noted more recently in newly industrialized regions. In contrast IBD is rare in most regions in SSA. For both diseases this may reflect under-reporting or limited access to diagnostic modalities, but an alternative explanation is the high burden of infection with gastrointestinal parasites endemic to SSA which may attenuate the risk of developing GCA and IBD. In this mini review we discuss the complex interplay between these microorganisms, GCA, and IBD, as well as a possible protective role of *H. pylori* and the development of IBD.

KEYWORDS

***Helicobacter pylori*, inflammatory bowel disease, gastric cancer, Africa, helminths**

Introduction

Gastric adenocarcinoma (GCA) is the 5th leading cancer globally and the 4th leading cause of cancer death worldwide. Data from the GLOBOCAN 2020 database estimated that 1.1 million cases of gastric cancer were diagnosed worldwide in 2020 with considerable geographic variation (1). Eastern Asian regions showed the highest

incidence rates in both males and females (age standardized rates of 32.5 and 13.2 per 100,000, respectively). About two thirds of all cases occur in men. Ninety percent of non-cardia GCAs are attributable to *Helicobacter pylori* (*H. pylori*) which is the most frequently encountered bacterial infection worldwide (2). Although data on *H. pylori* prevalence in SSA is limited, a 2016 systematic review with meta-analysis including 184 studies and evaluating the prevalence of *H. pylori* infection worldwide, found that Africa had the highest rate with a prevalence of 70.1% (2). In another meta-analysis Nigeria was found to have the highest prevalence globally with a rate of 89.7% (3). Despite this the number of reported cases of GCA in SSA is surprisingly low. The GLOBOCAN data base reported age standardized GCA rates between 4.6 to 4.9 and 2.4 to 4.2 per 100,000 in men and woman, respectively from SSA (1).

A similar phenomenon is seen with the inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC). These are chronic inflammatory disorders of the gastrointestinal tract, characterized by periods of remission and intercurrent flares of disease activity. IBD is thought to result from complex interactions between environmental factors (such as tobacco and diets high in animal fats or processed foods), in a genetically susceptible host, resulting in an aberrant immune response to the intestinal flora (4, 5). These disorders have risen dramatically over the past century in high income countries across the globe, with sharp increases noted more recently in newly industrialized regions (6, 7). In contrast IBD is rare in most regions in SSA (8–10).

For both diseases the relative paucity of cases may reflect under-reporting or limited access to diagnostic modalities, but an alternative explanation is the high burden of infection with gastrointestinal parasites endemic to SSA which may attenuate the risk of developing GCA and IBD (11, 12).

Soil-transmitted helminth (STH) infections are widespread in SSA as a consequence of poor socioeconomic status and environmental sanitation. The most common STHs are *Trichuris trichiura*, *Ascaris lumbricoides*, and the hookworms (*Necator americanus* and *Ancylostoma duodenale)*. Infection with these STHs modulates host immune responses, induces systematic immune tolerance, and suppresses inflammatory responses (11, 12).

Gastric cancer in SSA

H. pylori and gastric cancer

The most established risk factor for intestinal GCA is *H. pylori*, with an attributable risk of 75–88% (13, 14). The mechanism involves an interplay between the host, gastric microenvironment, and bacterial virulence factors (15). These strain-specific virulence factors, cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), are not only involved in the induction and maintenance of inflammatory responses, but enable the colonization and survival of *H. pylori* within the gastric mucosa, leading to further immune escape, the induction of premalignant alterations and eventually GCA (15, 16). Histologically, based on the Lauren classification, there are four types of GCA: the intestinal type (by far the commonest), diffuse type, mixed and indeterminate, or unclassifiable subtypes (17). Intestinal GCA specifically, progresses in the stomach through the Correa sequence, with a stepwise linear progression from chronic gastritis, gastric atrophy, gastric intestinal metaplasia, dysplasia and finally, invasive cancer (18). Lending credence to its importance, this original model was amended to involve the role of *H. pylori* as the prime causative environmental agent (19).

The "African enigma" and role of helminths

Published literature, however, suggest that GCA appears to be rare, or not as high as would be expected in Africa. This is in the context that more than two thirds of the population in SSA have *H. pylori* infection (20). This dissociation has been famously termed the "African enigma" by Holcombe et al. (21) on the basis that based on data the rate of occurrence of GCA in some regions of Africa is roughly between a low 2 and 3%. These low rates he argues, may be due to acquisition of infection in childhood, which confers a less pathogenic inflammatory phenotype, the low rate of intestinal metaplasia (a precursor to GCA), and protective environmental factors such as low rates of smoking and a nutritious diet of vegetables in Africa. Further arguments proposed to support this theory by others include host factors and the high burden of parasitic infections which may bias the inflammatory cytokine response to a Th2 type (22). The latter argument was originally based on animal studies; the first showed that co-infection with nematodes in mice with *H. pylori* protects against gastric atrophy (23). It is reported that concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces *H. pylori*-induced gastric atrophy. This is mediated by downregulation of TNFα and IL1β, and upregulation of IL4 and IL10 (23). In a later study, these findings were corroborated in *H. pylori* infected transgenic mice, where co-infection with helminths resulted in similar degrees of inflammation, but reduced gastric atrophy ($p < 0.04$) and dysplasia ($p < 0.02$) (24). Few studies have been conducted in the adult human population, with no studies in SSA. Notwithstanding, a recent study performed in Venezuela, was the first to show that co-infection with *H. pylori* and intestinal helminths was associated with increased IL4 expression, together with lower degrees

of inflammation and gastric atrophy, compared to mono-infected patients (25). Similarly, in a study from Colombia (a high endemic area for parasites), with virulence-associated genotypes of *H. pylori*, the rate of GCA was low, suggesting a modulating role of the immune system by helminths (26). In a third 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 (27), again supporting the role of helminths in potentially explaining the enigma. In Brazil, however, this association was not found; although co-infection with parasites was as high as 15% in adults, polarization of the immune system toward a Th1 or Th2 response was independent of co-infection (28), throwing into doubt the findings of previous studies. Although these countries are similar in economic development to SSA, unfortunately no studies have been conducted in SSA. As such, only inferences can be made regarding the potential role of helminths in explaining the enigma. More recent data from SSA, however, reports that those with African ancestry demonstrate co-evolution with *H. pylori* compared to their European counterparts, in whom this appears to be maladapted (29). This finding suggests that *H. pylori* may be "less pathogenic" in this population, thus explaining the enigma possibly based on co-infection with parasites, the gastric microbiome or dietary factors.

Notwithstanding the above explanations, to date, however, this hypothesis has not been fully elucidated, with some questioning its existence (30). Detractors of this theory argue that it is not uncommon for infectious disease to present with variable clinical expressions in different regions, and that GCA would be expected in regions with longer life expectancy (which has not been the case in SSA), and higher rates of atrophic gastritis. Furthermore, they argue that rather than focus on individual populations, it is the convergence of factors (bacterium, host and environmental factors), that play a role in disease expression (30). Finally, they argue that the low rates of GCA may merely reflect selection bias of studies that include populations with limited access to endoscopy and limited data for explanations such as *H. pylori* strain and the role of parasites in modulating the immune response toward a Th2 phenotype. Hence these authors posit that rather than a hypothesis based on experimental data, this enigma is a myth. The lack of data, however, makes this assertion difficult to make, but interesting as potential for future research.

To summarize, inconsistent data is the key limiting factor in the argument for or against the enigma. However, given the high prevalence of helminth infections in SSA (28, 31) this provides a niche area of research not only in terms of understanding the pathophysiology of *H. pylori*, the enigma more specifically, but also the potential for using helminths as a therapeutic tool in preventing GCA (and potentially other gastrointestinal cancers) not just in SSA, but worldwide.

Inflammatory bowel disease (IBD) in SSA

Inflammatory bowel disease has largely been a disease affecting high-income countries; in particular North America and Europe. Over recent years an increase in cases of newly diagnosed IBD has also been reported in North Africa, Asia, and South America (6, 7).

In contrast, apart from South Africa, IBD has been considered rare in SSA. The recent Global Burden of Disease study reported age standardized prevalence rates in SSA ranging between 9.9 and 11.2 per 100,000 population (10). These rates are in stark contrast with Westernized countries such as North America, where a prevalence of 442 per 100,000 people was reported for 2017 (10). Two systematic reviews published in 2020 identified fewer than 250 published cases of IBD in SSA, after excluding those from SA (8, 9). This paucity of cases may represent under reporting or misdiagnosis due to a high burden of infectious diseases in the sub-continent which can mimic IBD, notably Amebiasis, Schistosomiasis, Strongyloidiasis, and Intestinal Tuberculosis (32). It may also reflect a different genetic disposition or low exposure to environmental risk factors described in high income populations. In addition, some cases of IBD in SSA might remain undetected because of a lack of awareness or limitations in diagnostic and clinical capacity (32).

Low rates of IBD may, however, also be explained by the high prevalence of chronic gut infections endemic in the region which appear to attenuate the risk of developing IBD, notably *H. pylori* and parasitic infestation with helminths. Both chronic infections induce systematic immune tolerance and suppress inflammatory responses. This is consistent with the hygiene hypothesis which proposes a causal relationship between increased sanitation leading to reduced exposure to microorganisms and an increase in autoimmune disease such as IBD (33).

H. pylori and IBD

In contrast to GCA several studies have shown a protective association between *H. pylori* infection and IBD. In a meta-analysis of 40 case-control studies, *H. pylori* exposure was associated with a significant reduction in the risk of developing IBD (OR 0.43, 95% CI 0.36–0.50) (34). This observation was stronger for CD than for UC. Similar findings have been reported in animal models, where *H. pylori* exposure has been associated with attenuation of experimental colitis (35, 36).

There are several biologically plausible mechanisms whereby *H. pylori* infection may protect against the development of IBD. Over millennia *H. pylori* has adapted to evade the hosts innate and adaptive immune responses, to maintain mucosal colonization. *H. pylori* infection appears

to induce a blunted Th1/Th17 response with an enhanced immunosuppressive T-reg response (37) and also induces tolerogenic dendritic cells (DCs) (36).

In a meta-analysis this protective effect of *H. pylori* was restricted to CagA-positive strains, with no significant difference in the risk of IBD between *H. pylori* CagA seronegative strains, and *H. pylori* non-exposed individuals (19). The beneficial effect of CagA positivity can be at least partly explained by the increased IL10 responses inducing semi-mature DC and higher T-reg responses (38). Of interest 95% of *H. pylori* strains in a South African study were CagA positive (39).

The inverse relationship between *H. pylori* infection and the development of IBD may, however, be confounded by many other factors implicated in the hygiene hypothesis in that the more sterile environment encountered in higher income regions reduces the likelihood of *H. pylori* infection (33, 40). It is unclear if treatment for *H. pylori* infection is associated with an increase in the risk of subsequently developing IBD as the evidence is conflicting (41, 42).

IBD and helminth infection

Soil-transmitted helminths such as *Ascaris lumbricoides*, *Trichuris trichiura*, and the hookworms *Ancylostoma duodenale* and *Necator americanus,* are endemic in SSA. These infections are transmitted by eggs present in human feces, which contaminate the soil, and as with *H. pylori* are associated with overcrowding, less industrialization, and poorer water sanitation, all of which may be protective of IBD (33, 43).

Similar to *H. pylori*, helminth infection appears to modulate the host response leading to a state of relative immune tolerance (44, 45). Infection by helminths has been shown to attenuate experimental colitis in mouse models as well as impact the composition of the gastrointestinal microbiome (46–48). There is also evidence from human studies that infections with tissue-dwelling helminths initiate expansion of T-regulatory (T_{reg}) cells that suppress both Th1 and Th2 effector responses and up-regulate the release of anti-inflammatory cytokines such as IL10 and transforming growth factor (TGFβ) (49). In a study of schoolchildren in Cameroon it was shown that levels of these regulatory cytokines correlate with the intestinal worm burden and that this elevation in anti-inflammatory cytokine secretion in peripheral blood induces immunological hypo-responsiveness (49). It has been hypothesized that worm-driven up-regulation of IL10 and or TGFβ secreting T_{reg} cells, represent a parasite survival strategy to suppress an effective host immune response.

An inverse association between helminth infections and the development of IBD in SSA has been described. A South African study of 151 patients with IBD showed that childhood helminth exposure was associated with 80% risk reduction for the development of IBD compared with controls (12).

Several studies have evaluated the efficacy of the pig whipworm *Trichuris suis* for the treatment of IBD with mixed results; initial reports were encouraging, however, a meta-analysis of *T. suis* ova in human clinical trials showed no statistically significant effect (50). However, the included studies were limited by small sample size which may have masked any potential benefit. The potential therapeutic benefit of helminth infection and helminth products is being further explored (51).

Conclusion

Gastric adenocarcinoma and IBD are common disorders globally, yet surprisingly low numbers of both disorders are reported in Sub-Saharan Africa (SSA). This may reflect under-reporting or limited access to diagnostic modalities, but an alternative explanation is the high burden of infection with gastrointestinal helminths, which may attenuate the risk of developing GCA and IBD through induction of immune tolerance. In contrast to GCA several studies have shown a protective association between *H. pylori* infection and IBD. Given the lack of high- quality data from SSA these observations require further investigation, as they may provide important insights that can be exploited for the development of diagnostic and/or therapeutic tools in the management of these conditions.

Author contributions

Both authors contributed equally to the conception, initial, and revised drafts of the manuscript, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T, et al. The current and future incidence and mortality of gastric cancer in 185 Countries, 2020-40: a population-based modelling study. *EClinicalMedicine.* (2022) 47:101404. doi: 10.1016/j.eclinm.2022.101404

2. Hooi JK, Lai WY, Ng WK, Suen MM, Underwood FE, Tanyingoh D, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology.* (2017) 153:420–9. doi: 10.1053/j.gastro.2017.04.022

3. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* (2018) 47:868–76. doi: 10.1111/apt.14561

4. Torres J, Mehandru S, Colombel J, Peyrin-Biroulet L. Crohn's disease. *Lancet.* (2017) 389:1741–55. doi: 10.1016/S0140-6736(16)31711-1

5. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J. Ulcerative colitis. *Lancet.* (2017) 389:1756–70. doi: 10.1016/S0140-6736(16)32126-2

6. Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. *Gastroenterology.* (2017) 152:313–21. doi: 10.1053/j.gastro.2016.10.020

7. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet.* (2017) 390:2769–78. doi: 10.1016/S0140-6736(17)32448-0

8. Watermeyer G, Epstein D, Adegoke O, Kassianides C, Ojo O, Setshedi M. Epidemiology of inflammatory bowel disease in sub-Saharan Africa: a review of the current status. *S Afr Med J.* (2020) 110:1006–9. doi: 10.7196/SAMJ.2020.v110i10.14489

9. Hodges P, Kelly P. Inflammatory bowel disease in Africa: what is the current state of knowledge? *Int Health.* (2020) 12:222–30. doi: 10.1093/inthealth/ihaa005

10. Gbd 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet Gastroenterol Hepatol.* (2020) 5:17–30. doi: 10.1016/S2468-1253(19)30333-4

11. Kumar S, Patel GK, Ghoshal UC. *Helicobacter pylori*-induced inflammation: possible factors modulating the risk of gastric cancer. *Pathogens.* (2021) 10:1099. doi: 10.3390/pathogens10091099

12. Chu KM, Watermeyer G, Shelly L, Janssen J, May TD, Brink K, et al. Childhood helminth exposure is protective against inflammatory bowel disease: a case control study in South Africa. *Inflamm Bowel Dis.* (2013) 19:614–20. doi: 10.1097/MIB.0b013e31827f27f4

13. Correa P, Houghton J. Carcinogenesis of *Helicobacter pylori*. *Gastroenterology.* (2007) 133:659–72. doi: 10.1053/j.gastro.2007.06.026

14. Correa P, Piazuelo MB. The gastric precancerous cascade. *J Dig Dis.* (2012) 13:2–9. doi: 10.1111/j.1751-2980.2011.00550.x

15. Baj J, Forma A, Sitarz M, Portincasa P, Garruti G, Krasowska D, et al. *Helicobacter pylori* virulence factors-mechanisms of bacterial pathogenicity in the gastric microenvironment. *Cells.* (2020) 10:27. doi: 10.3390/cells10010027

16. Polk DB, Peek R Jr. *Helicobacter pylori*: gastric cancer and beyond. *Nat Rev Cancer.* (2010) 10:403–14. doi: 10.1038/nrc2857

17. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand.* (1965) 64:31–49. doi: 10.1111/apm.1965.64.1.31

18. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. *Lancet.* (1975) 2:58–60. doi: 10.1016/S0140-6736(75)90498-5

19. Correa P. A human model of gastric carcinogenesis. *Cancer Res.* (1988) 48:3554–60.

20. Geraghty J, Thumbs A, Kankwatira A, Andrews T, Moore A, Malamba R, et al. *Helicobacter pylori*, HIV and gastric hypochlorhydria in the malawian population. *PLoS One.* (2015) 10:e0132043. doi: 10.1371/journal.pone.0132043

21. Holcombe C. *Helicobacter pylori*: the African enigma. *Gut.* (1992) 33:429–31. doi: 10.1136/gut.33.4.429

22. Ghoshal UC, Chaturvedi R, Correa P. The enigma of *Helicobacter pylori* infection and gastric cancer. *Indian J Gastroenterol.* (2010) 29:95–100. doi: 10.1007/s12664-010-0024-1

23. Fox JG, Beck P, Dangler C, Whary M, Wang T, Shi H, et al. Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces *helicobacter*-induced gastric atrophy. *Nat Med.* (2000) 6:536–42. doi: 10.1038/75015

24. Whary MT, Muthupalani S, Ge Z, Feng Y, Lofgren J, Shi HN, et al. Helminth co-infection in *Helicobacter pylori* infected INS-GAS mice attenuates gastric premalignant lesions of epithelial dysplasia and glandular atrophy and preserves colonization resistance of the stomach to lower bowel microbiota. *Microbes Infect.* (2014) 16:345–55. doi: 10.1016/j.micinf.2014.01.005

25. Fuenmayor-Boscán A, Hernández-Rincón I, Arismendi-Morillo G, Mengual E, Rivero Z, Romero G, et al. Changes in the severity of gastric mucosal inflammation associated with *Helicobacter pylori* in humans coinfected with intestinal helminths. *Indian J Gastroenterol.* (2020) 39:186–95. doi: 10.1007/s12664-020-01023-0

26. Bravo LE, Doom L v, Realpe JL, Correa P. Virulence-associated genotypes of *Helicobacter pylori*: do they explain the African enigma? *Am J Gastroenterol.* (2002) 97:2839–42. doi: 10.1111/j.1572-0241.2002.07031.x

27. Du Y, Agnew A, Ye X, Robinson PA, Forman D, Crabtree JE. *Helicobacter pylori* and *Schistosoma japonicum* co-infection in a Chinese population: helminth infection alters humoral responses to H. pylori and serum pepsinogen I/II ratio. *Microbes Infect.* (2006) 8:52–60. doi: 10.1016/j.micinf.2005.05.017

28. Bravo LE, Matta AJ, Restrepo-Avenia JM. [Immune response Th1/Th2 to *Helicobacter pylori* and Helminths in co-infected patients]. *Rev Chil Pediatr.* (2020) 91:363–70. doi: 10.32641/rchped.v91i3.1431

29. Cavadas B, Leite M, Pedro N, Magalhães A, Melo J, Correia M, et al. Shedding light on the African enigma: in vitro testing of homo sapiens-*Helicobacter pylori* coevolution. *Microorganisms.* (2021) 9:240. doi: 10.3390/microorganisms9020240

30. Graham DY, Lu H, Yamaoka Y. African, Asian or Indian enigma, the East Asian *Helicobacter pylori*: facts or medical myths. *J Dig Dis.* (2009) 10:77–84. doi: 10.1111/j.1751-2980.2009.00368.x

31. Cherian S, Burgner DP, Cook AG, Sanfilippo FM, Forbes DA. Associations between *Helicobacter pylori* infection, co-morbid infections, gastrointestinal symptoms, and circulating cytokines in African children. *Helicobacter.* (2010) 15:88–97. doi: 10.1111/j.1523-5378.2009.00740.x

32. Watermeyer G, Katsidzira L, Setshedi M, Devani S, Mudombi W, Kassianides C, et al. Inflammatory bowel disease in sub-Saharan Africa: epidemiology, risk factors, and challenges in diagnosis. *Lancet Gastroenterol Hepatol.* (2022) 7:952–61. doi: 10.1016/S2468-1253(22)00047-4

33. Garn H, Potaczek DP, Pfefferle PI. The hygiene hypothesis and new perspectives-current challenges meeting an old postulate. *Front Immunol.* (2021) 12:637087. doi: 10.3389/fimmu.2021.637087

34. Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos G, Lytras T, Bonovas S. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. *Gastroenterology.* (2019) 157:647–59. doi: 10.1053/j.gastro.2019.04.016

35. Zhang H, Dai Y, Liu Y, Wu T, Li J, Wang X, et al. *Helicobacter pylori* colonization protects against chronic experimental colitis by regulating Th17/Treg balance. *Inflamm Bowel Dis.* (2018) 24:1481–92. doi: 10.1093/ibd/izy107

36. Luther J, Owyang SY, Takeuchi T, Cole TS, Zhang M, Liu M, et al. *Helicobacter pylori* DNA decreases pro-inflammatory cytokine production by dendritic cells and attenuates dextran sodium sulphate-induced colitis. *Gut.* (2011) 60:1479–86. doi: 10.1136/gut.2010.220087

37. Yu Y, Zhu S, Li P, Min L, Zhang S. *Helicobacter pylori* infection and inflammatory bowel disease: a crosstalk between upper and lower digestive tract. *Cell Death Dis.* (2018) 9:961. doi: 10.1038/s41419-018-0982-2

38. Kaebisch R, Mejías-Luque R, Prinz C, Gerhard M. *Helicobacter pylori* cytotoxin-associated gene A impairs human dendritic cell maturation and function through IL-10-mediated activation of STAT3. *J Immunol.* (2014) 192:316–23. doi: 10.4049/jimmunol.1302476

39. Kidd M, Lastovica AJ, Atherton JC, Louw JA. Heterogeneity in the *Helicobacter pylori* vacA and cagA genes: association with gastroduodenal disease in South Africa? *Gut.* (1999) 45:499–502. doi: 10.1136/gut.45.4.499

40. Ozbey G, Hanafiah A. Epidemiology, diagnosis, and risk factors of *Helicobacter pylori* infection in children. *Euroasian J Hepatogastroenterol.* (2017) 7:34–9. doi: 10.5005/jp-journals-10018-1208

41. Lin K, Chiu G, Waljee AK, Owyang SY, El-Zaatari M, Bishu S, et al. Effects of anti-*Helicobacter pylori* therapy on incidence of autoimmune diseases, including inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* (2019) 17:1991–9. doi: 10.1016/j.cgh.2018.12.014

42. Tanner S, Katz J, Cominelli F, Regueiro M, Cooper G, Mansoor E. Inflammatory bowel disease and *Helicobacter pylori*: protective or present? *Inflamm Bowel Dis.* (2022):izac202. doi: 10.1093/ibd/izac202

43. Sartorius B, Cano J, Simpson H, Tusting LS, Marczak LB, Miller-Petrie MK, et al. Prevalence and intensity of soil-transmitted helminth infections of children in sub-Saharan Africa, 2000-18: a geospatial analysis. *Lancet Glob Health.* (2021) 9:e52–60. doi: 10.1016/S2214-109X(20)30398-3

44. Gazzinelli-Guimaraes PH, Nutman TB. Helminth parasites and immune regulation. *F1000Res.* (2018) 7:F1000FacultyRev–1685. doi: 10.12688/f1000research.15596.1

45. King IL, Li Y. Host-parasite interactions promote disease tolerance to intestinal helminth infection. *Front Immunol.* (2018) 9:2128. doi: 10.3389/fimmu.2018.02128

46. Cançado GG, Fiuza JA, Paiva NC, Lemos L d, Ricci ND, Gazzinelli-Guimarães PH, et al. Hookworm products ameliorate dextran sodium sulfate-induced colitis in BALB/c mice. *Inflamm Bowel Dis.* (2011) 17:2275–86. doi: 10.1002/ibd.21629

47. Elliott DE, Setiawan T, Metwali A, Blum A, Urban JF Jr, Weinstock JV. Heligmosomoides polygyrus inhibits established colitis in IL-10-deficient mice. *Eur J Immunol.* (2004) 34:2690–8. doi: 10.1002/eji.200324833

48. Reynolds LA, Finlay BB, Maizels RM. Cohabitation in the intestine: interactions among helminth parasites, bacterial microbiota, and host immunity. *J Immunol.* (2015) 195:4059–66. doi: 10.4049/jimmunol.1501432

49. Turner JD, Jackson JA, Faulkner H, Behnke J, Else KJ, Kamgno J, et al. Intensity of intestinal infection with multiple worm species is related to regulatory cytokine output and immune hyporesponsiveness. *J Infect Dis.* (2008) 197:1204–12. doi: 10.1086/586717

50. Huang X, Zeng L, Chen F, Zhu J, Zhu M. Trichuris suis ova therapy in inflammatory bowel disease: a meta-analysis. *Medicine.* (2018) 97:e12087. doi: 10.1097/MD.0000000000012087

51. Arai T, Lopes F. Potential of human helminth therapy for resolution of inflammatory bowel disease: the future ahead. *Exp Parasitol.* (2022) 232:108189. doi: 10.1016/j.exppara.2021.108189