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Cichlid fishes are promising underutilised models to investigate helminth-microbiome interactions

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Abstract

The "Old Friends Hypothesis" suggests that insufficient early exposure to symbionts may hinder immune development, contributing to increased immune-related diseases in the Global North. While the microbiome is often the focus, helminths, which may also offer health benefits, receive little attention. The infection and effect of helminths, in turn, are influenced and may be even determined by micro-organisms. The mechanisms behind general parasite-microbiome interactions are poorly understood, despite their profound implications on the health of their hosts. Because these interactions are typically studied for single helminth species in laboratory animal models, the important aspect of helminth diversity remains overlooked in this context. A literature search for research on the relationship between host helminth diversity and microbial diversity, resulted in 27 publications; most focused on human or other mammalian hosts, and relied on natural exposure rather than experimental inoculation with helminths. Almost half of these studies did not empirically investigate health outcomes for the host. This understudied potential warrants consideration for additional candidate model systems. In view of the high burden of helminthiasis, and the high species diversity of helminths, we propose to seek these models in the Global South, where a considerable proportion of research on community diversity aspects of helminth-microbiome interactions took place. The low availability of genomic resources for parasitic worms in many regions of the Global South, however, calls for more integrative helminthological research efforts. Given the substantial similarities in immune systems, several fishes are models for human health and disease. More effort could be done to also establish this for cichlids, the representatives of which in the African Great Lakes would provide a well-delineated, closed natural system with relevance to human health in view of fish-borne zoonoses and other water-borne parasites. Moreover, a good baseline exists in terms of these cichlids' genomics, parasitology, and microbiology. We therefore call for the exploration of African Great Lake cichlids as model hosts to understand the interactions between microbial diversity, helminth diversity, and host health.

Keywords

health; immunomodulation; Lake Tanganyika; microbial diversity; symbiome; Old Friends Hypothesis; parasite; worm

1) Introduction

From birth onwards, humans are colonized by microorganisms including fungi, protozoans and viruses (Jackson et al. 2009). In addition, humans have coexisted with helminths for most of our existence (Ferreira et al. 1984). Yet, since the industrial era, countries in the Global North have established a reduction in prevalence of helminths and other parasites (Loker 2013, Ryan et al. 2022). Additionally, studies have observed an association between industrial lifestyles and reduced diversity in the gut microbiome (De Filippo et al. 2010). Allergic disorders and inflammatory conditions increased throughout the 20th century in the Global North (Eder et al. 2006, Conrad et al. 2023). From the late 19th century, hay fever was increasingly reported in wealthy urban populations, while farming communities remained less affected (Blackley 1873). As living conditions have changed, these trends indicate a disturbance in immune regulation, leading to a disbalanced response to harmless allergens or infections.

The "Old Friends Hypothesis" provides an evolutionary view on the rise of immune-related disorders like allergies, asthma, and autoimmune diseases, including a focus on early life (Rook 2023). It describes that the absence or reduced exposure to specific microorganisms or helminths in early life, which co-evolved with humans as hunter-gatherer omnivores, disrupts normal immune system development. This may lead to a disturbance of immunoregulation due to insufficient exposure to microorganisms or helminths that drive the expansion of components such as regulatory T cells (Rook et al. 2004). The hypothesis suggests that exposures to specific organisms are critical for properly training the immune system to differentiate between harmful and benign antigens, and preventing excessive immune responses. For example, lipopolysaccharide, a component of the outer membrane of gram-negative bacteria, may protect against allergic responses by inducing the ubiquitin-modifying enzyme A20 in lung epithelial cells (Schuijs et al. 2015). Also helminths seem to fit the narrative of the “Old Friends Hypothesis”. For instance, helminth infections may also confer protective benefits against autoimmune diseases, allergies, and inflammatory disorders by promoting immune tolerance through immune system modulation and microbiome alterations (Giacomin et al. 2015, Versini et al. 2015, Maizels et al. 2018). In laboratory animal models, helminth infections have been linked to suppression of pro-inflammatory gut bacteria, leading to protection against Crohn’s disease in genetically susceptible mice (Ramanan et al. 2016). Similarly, in humans, helminth infections have been shown to increase microbial diversity and alter antibody levels, although the full extent of these effects is still not well understood (Yang et al. 2017). Infection with pinworms (*Enterobius vermicularis*) was shown to be associated with a protective effect on the development of clinical malaria in Tanzanian children, while infection with hookworm exacerbates the severity of malaria (Salim Masoud et al. 2024).

Several studies indicate that helminth infections are linked to increased gut microbiota diversity and significant changes in its composition (Rausch et al. 2018, Lee et al. 2019, Rafaluk-Mohr et al. 2022). These shifts in the microbiome could affect the risk for various diseases, such as asthma, viral infections, and metabolic disorders (Sanya et al. 2020, Zheng et al. 2020). Furthermore, the microbiome plays a role in the establishment of certain helminth infections and can influence their progression (Hayes et al. 2011). Specific bacterial taxa have been found to affect an individual’s resistance or susceptibility to helminths (Dea-Ayuela et al. 2008), though the precise mechanisms underlying these helminth-microbiota interactions remain largely unclear. Despite the promising findings that infection with helminth parasites alleviates symptoms of various diseases, our understanding of the mechanisms underlying the interaction between parasites and the microbiome remains limited.

2) The study of microbiome-parasite interactions needs more attention for parasite and host diversity, which relies on natural exposure

Despite their interconnected roles in host health, microbes and parasites have traditionally been studied in isolation, overlooking their collective contribution as part of a “symbiome”. We regard the term “symbiont” (and collectively “symbiome”) as referring to any host-associated

organisms (including viruses), which can have negative, neutral, or positive interactions with the host (Bass et al. 2021).
According to the holobiont concept (Margulis & Fester 1991, Baedke et al. 2020), the symbionts and the host act as a unique biological entity termed “holobiont”, a unit of selection in evolution (Zilber-Rosenberg & Rosenberg 2008). Consequently, the “hologenome” is the collective of genomes of host and symbiome, with interactions between hologenome and environment determining phenotype and being pivotal to adaptation and evolution (Madhusoodanan 2019, González-Pech et al. 2024). Symbiome genomes can change rapidly under environmental stress and therefore buy the host precious time to adapt and survive (Rosenberg & Zilber-Rosenberg 2018). Hologenomic approaches might be applied as part of the One Health approach for in-depth ecosystem health assessments in real-time (Urban et al. 2023) and in aquaculture to enhance growth, health and overall production sustainability (Limborg et al. 2018). Unfortunately, in spite of being an integral part of the holobiont, the role of parasites in this intricate evolutionary unit has been largely ignored.

Parasites, including helminths, inhabit diverse niches within their hosts, where they inevitably encounter a plethora of commensal, mutualistic and pathogenic microorganisms. These interactions can significantly influence the host immune response, metabolism, overall health and development, both in animal models and humans (Giacomin et al. 2015, Versini et al. 2015, Zaiss & Harris 2016, Piazzesi & Putignani 2022). Despite recent progress (Brosshot & Reynolds 2018, Loke & Harris 2023, Rooney et al. 2023), our understanding of the molecular and cellular mechanisms governing parasite-microbiome dynamics remains limited. Addressing this gap is crucial, as the interplay between parasites and the microbiome might have far-reaching effects on progression of diseases, effectiveness of therapeutic interventions, and development of novel treatments.

Helminths secrete various immunomodulatory molecules that can impact the host immune system directly or alter the composition and function of the (gut) microbiota (Maizels et al. 2018, Yeshi et al. 2022), potentially creating environments more favorable for the parasite while dampening host immune responses. Conversely, certain microbiota may influence parasite colonization and pathogenicity, implying a bidirectional relationship (Loke & Harris 2023). Exploring these parasite-microbiome interactions is essential not only for advancing our understanding of parasitology but also for unlocking new avenues in microbiome research and therapeutic innovation. These may lead to novel microbiome-targeted strategies for managing parasitic infections and novel interventions/treatments that harness the beneficial effects of helminths. Unfortunately, research on the microbiome associated with helminths or other parasites has not kept track with the general surge in microbiomes studies (Salloum et al. 2023).

The importance of microbial community composition and the beneficial role of a diverse microbiome on health outcomes of animals, plants, and ecosystems are well-established (e.g., Li et al. 2018, Peixoto et al. 2021). For instance, they may determine the resilience of a host or ecosystem to environmental perturbations (Dunphy et al. 2021, Potts et al 2022). The literature on helminth-microbiota interactions, however, typically focuses on laboratory-kept hosts and single-species infections of helminths (Kreisinger et al. 2015), overlooking the aspect of parasite diversity at the species and genomic level. To assess the extent to which diversity is taken into account in the study of microbiome-helminth interactions, we performed a search on Web of Science. The search for research on the relationship between host helminth diversity and microbial diversity, resulted in 244 initial hits and was filtered to 27 relevant studies based on specific criteria such as focus on empirical work, relevance to parasitic worms, and inclusion of helminth diversity, while categorizing these studies by host taxa, health outcomes, and type of helminth exposure (natural or experimental) (Figure 1). Twenty-seven publications were retained, which indicates that only a minority of studies on microbiome-parasitic worm interactions includes aspects of helminth (species) diversity. Several studies mentioned the presence of multiple species of helminths or other parasite taxa, while investigating the microbial interactions with a single one (Prommi et al. 2020, Martínez-Mota et al. 2021, Doolin et al. 2022). Figure 1 details the state of empirical research about the relationship between the diversity of helminths of a host and its microbial diversity. Out of the 27 retained studies, 22 investigated human or other mammal hosts (Figure 1A). Only just over half of the studies verified health outcomes for the host (Figure 1B). Only one publication investigated helminth infections resulting from experimental exposure (Figure 1C).

The influence of the host's environment and behaviour on its symbionts makes it hard to mimic a real-life symbiome, or natural exposure to symbionts (Oyesola et al. 2022), experimentally. Indeed, the microbiomes of conspecific natural and captive (including laboratory) animal populations are known to differ (e.g. Rosshart et al. 2017, Clavere-Graciette et al. 2022), as do the microbial and parasite load between rural and urban populations (Rouffaer et al. 2017, Flandroy et al. 2018, Vanhove et al. 2021). Moreover, in humans and other animals, lifestyle and environment are key factors in determining microbiome composition (Von Hertzen et al. 2011, Glendinning et al. 2014, Bahrndorff et al. 2016, Campbell & Wisniewski 2017, Riggs et al. 2018). Therefore, approaches going beyond laboratory conditions gained traction in immunology (Graham 2021) and may be highly relevant to studying the symbiome. For instance, releasing test animals into a semi-natural environment, or oral inoculation, may allow fungal colonisation enriching the intestinal microbiota (Chen et al. 2023). Such approaches are also promising when studying helminth infections and their immune responses: they allow taking into account host and environmental factors that facilitate translation to a natural context. Hence, although experiments are definitely needed to reveal the mechanisms behind helminth-microbiome interactions (Formenti et al. 2020), it remains hard to include the diversity of helminths into experimental approaches. Unsurprisingly, in our literature sample, only a single study applied experimental co-infection: Bonde et al. (2023) inoculated pigs with the nematodes *Ascaris suum* and *Oesophagostomum dentatum*. This clearly illustrates that both correlational and experimental investigations of helminth-microbiota interactions rely on natural host populations when the entire helminth community is to be considered. Unfortunately, such studies are scarce (Kreisinger et al. 2015) and it is timely to propose additional suitable candidate models to study the health and disease outcomes of helminth-microbiome interactions.

3) Candidate models to study helminth-microbiome interactions should be found in the Global South

We mapped the geographical distribution of the helminth-microbiome studies which take into account the diversity of helminths (resulting from the above-mentioned Web of Science search). Figure 2 shows where the empirical research took place, across the regional groupings in the framework of the Sustainable Development Goals[1]. We compared this with the state of exploration of helminth diversity and the availability of genetic resources (Figure 2A) (Poulin et al. 2019), and with the prevalence of cysticercosis (caused by the tapeworm *Taenia solium*), as a proxy for the burden of helminthiases (Figure 2B).
While the total number of studies retained in our search is low, they appear quite evenly spread across the globe (Figure 2). It is noteworthy that the Global South has seen a comparable amount of research attention in this field. In this region the known and estimated helminth diversity are highest (Figure 2A), as is the maximal expected proportion of undiscovered helminth species (Carlson et al. 2020). It is also where the highest cysticercosis prevalences are found (Figure 2B). Indeed, although next to cysticercosis there are other helminthiases that occur in the Global North and South (e.g., ascariasis caused by nematode species belonging to *Ascaris*: Gazzinelli-Guimarães et al. 2021), the highest toll of helminthiases is typically found in the Global South and Africa in particular (Lustigman et al. 2012, Torgerson et al. 2015). Therefore, it is fitting that the latter continent is well-covered in certain areas of helminthology, such as geospatial mapping of human helminthiasis (Schluth et al. 2023).

On the other hand, the relative lack of genetic resources in many parts of the Global South, especially sub-Saharan Africa (Figure 2A) suggests that its considerable helminth diversity has been insufficiently studied, particularly with regard to modern integrative approaches. This

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[1] https://unstats.un.org/sdgs/indicators/regional-groups/

complicates helminth microbiome research and its translation into practice, as it limits, for instance, the possibility to diagnose and identify species and strains by molecular means. Globally, metabarcoding initiatives have done little to mitigate this situation, as they contributed rather to our understanding of occurrences of different microbial (e.g. Papaiakovou et al. 2022) and helminth communities (reviewed in Miller et al. 2024) than patterns of their potential reciprocal interactions. Thus, we second calls for more parasitological research in the Global South (Robertson et al. 2020); needless to say, this includes capacity development and technology transfer (e.g. Scholz et al. 2018). In particular, the situation in Africa shows the highest contrast between the available helminth genetic resources and helminth disease burden (Figure 2) (see also Pullan et al. 2014). We believe that work on how helminth diversity patterns influence helminth-microbe interactions would be best served by synergies between helminthologists and biomedical researchers (immunologists, epidemiologists…) focusing on host populations under natural exposure.

4) Proposal for a fish host model to study helminth-microbiome interactions in real-life settings

Fish models provide effective platforms for understanding the mechanisms and developing therapeutic agents for various human conditions, for instance cancer, cardiovascular, bone, renal and blood diseases (Adhish & Manjubala 2023), and hypercholesterolemia (Gora et al, 2023). They are also well-established for infectious diseases (Goody et al. 2014, Sanders et al. 2015, Misner et al. 2024), including those directly influenced by microbial communities (Flores et al. 2019). A key advantage is that fish gut microbiomes can be easily manipulated to establish the link between host symbiome diversity and disease processes (Gupta et al. 2019).

Several factors contribute to the establishment of many (tropical) fish species as invaluable laboratory models, namely short generation time (enabling individual monitoring throughout lifespans in experimental settings; in some species even multigenerational studies are possible in the time frame of typical research projects), high fecundity rate and external development, which facilitate genetic and functional studies. Moreover, genome assemblies of many fish species are publicly available[2]. Overall, the gene complements of fishes and tetrapods, including humans, are sufficiently conserved to allow insights into molecular mechanisms obtained in the former to inform our understanding in the latter, including aspects of the immune system. Remarkably, approximately 82% of the genes that have been linked to human diseases have counterparts (i.e., orthologues) in the zebrafish (*Danio rerio*) genome (Howe et al. 2013). Overall, these features facilitate possibilities of precision genome editing to design human disease models. Tessadori et al. (2018) introduced patient alleles in their zebrafish orthologues to model specific cardiovascular disorders, enabling the development of novel therapeutic strategies.

The zebrafish is the most widely recognised fish model of human diseases (Adhish & Manjubala 2023) but not the only one. Teleost fishes, the largest and most diverse group of vertebrates, exhibit an extraordinary range of specialised phenotypes that reflect their adaptation to a wide array of ecological niches (Parey et al. 2023). Due to its unique life cycle, the turquoise killifish (*Nothobranchius furzeri*), for instance, has emerged as a model for studying ageing and age-related neurological diseases (Kodera & Matsui 2022). Medaka (*Oryzias latipes*) serves as a model for neurodegenerative conditions like Parkinson's disease (Matsui et al. 2012). Recently, unusual fish evolutionary mutant models have gained popularity for phenotypes that mimic maladaptive human diseases but are beneficial for the species' adaptation to its environment (Beck et al. 2022). Elephantfishes (mormyrids) and knifefishes (gymnotiforms) have experienced numerous natural mutations in the ion channel gene *scn4aa*, making them excellent species for modelling channelopathies affecting skeletal muscle (Saunders & Gallant 2024). Other examples of fish evolutionary mutant models include the hybrid *Xiphophorus* (*X. maculatus* x *X. helleri*) (Schartl & Yu 2024), the mummichog

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[2] https://www.ensembl.org

(*Fundulus heteroclitus*) (Baris et al. 2017) and the Mexican cavefish (*Astyanax mexicanus*) (McGaugh et al. 2020), as models of malignant melanoma, mitochondrial, and diabetes and metabolic diseases, respectively.

We propose that fishes, currently only represented by a single study in our sample (Figure 1A), are an ideal system to observationally and experimentally study helminth-microbiome interactions and their effect on host health. Fishes are the ecologically dominant vertebrates in many aquatic environments (Helfman et al. 2009). Their immune systems, while simpler than those of mammals, share key components with humans (Rauta et al. 2012). This similarity allows for investigating how parasitic infections and microbiome changes impact the immune system, thereby enhancing our general understanding of how such interactions influence health outcomes.

Given the need for natural candidate models and helminthological research in the Global South in general and in Africa in particular (Figure 2), and the above-mentioned potential of fishes, we propose that a well-delineated aquatic system in the tropics, such as the African Great Lakes, could provide an ideal system to investigate helminth-microbiome interactions under natural conditions. Disease burden of tropical water-borne diseases is societally relevant in the region (Robertson et al. 2020) and contact with water as homogeniser exposes the human population to the same naturally occurring parasites as other potential hosts in the ecosystem. The increasing availability of high-quality reference fish genomes facilitates the application of various -omics approaches, especially for cichlid fishes (Brawand et al. 2014, Irisarri et al. 2018, Matschiner et al. 2020, Ronco et al. 2021), the most species-rich fish taxon in these lakes (Salzburger et al. 2014). Cichlids have been proposed as models for both non-communicable (Parsons et al. 2021) and infectious diseases, with the African Great Lake cichlids among the best-studied ones in terms of metazoan parasitological baseline (Vanhove et al. 2024). Also other cichlid species, especially economically important ones such as Nile tilapia and other tilapias, are well-studied parasitologically (Cruz-Laufer et al. 2021, Shinn et al. 2023), though health aspects are rarely considered (Shigoley et al. 2024). Moreover, also the microbial symbionts of (African Great Lake) cichlids have recently seen a surge in scientific attention (Riera & Baldo 2020, Costa et al. 2021). As such, fishes, especially in these lakes, provide a well-suited platform for experimentally manipulating both microbiomes and parasitic load, enabling researchers to uncover causal relationships and test potential therapeutic interventions relevant to human health.

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Figure captions

Figure 1. Characterisation of empirical research about the relationship between the diversity of helminths of a host and its microbial diversity, based on the following Web of Science search string on 27 August 2024: “diversity AND microb*” (Topic) NOT “Review OR Editorial Material” (Document Type) AND “helminth OR trematod* OR fluke OR cestod* OR tapeworm OR digenean OR monogen* OR nematod* OR acanthocephalan OR worm OR leech OR hirud*” (Topic) AND “health” (Topic). From the resulting 244 hits, 27 were retained, and 179 were not considered either because they did not contain empirical work (they were e.g. a review paper, perspective paper, proceedings paper, database paper, meta-analysis, or methodological paper), or because they did not deal with parasitic worms at all, or only studied helminths in the context of plant parasites, environmental samples, or waste(water). A further 38 were not retained because helminth diversity was not taken into consideration, i.e. these studies either focused on a single species, considered all helminth infections together, or only lumped several species into a single higher-order taxon. For the 27 studies retained, **(A)** shows the distribution over focal host taxa; **(B)** indicates whether studies look at health outcomes for the host, which we considered to be the case when host health was empirically studied, beyond the mere presence or clearance of infection; **(C)** compares whether studies applied experimental infection or relied on natural exposure to helminths.

Figure 2. Global distribution of empirical research about the relationship between the diversity of helminths of a host and its microbial diversity (see legend of Figure 1 for search string) across regional groupings used for indicators and reporting regarding the Sustainable Devevelopment Goals (https://unstats.un.org/sdgs/indicators/regional-groups/). **(A)** Proportional research effort on helminth and microbial diversity (left half-circles) compared to recent research effort on helminths relative to their known diversity in a given regional grouping (right half-circles). For the latter, we divided the number of available nucleotide sequences on NCBI GenBank per region, by the aggregated total for the region of per-country data of host-helminth records, based on the data and analyses from Poulin et al. (2019). This provides an estimate of genetic research effort relative to the regional helminth diversity; in a region where this proportion is low, the helminth diversity has not been adequately studied with recent molecular tools. **(B)** Proportional research effort on helminth and microbial diversity (left half-circles) compared to aggregated per-country prevalence of cysticercosis (per 100 000 people, based on data from the Global Burden of Disease study, Institute for Health Metrics and Evaluation, taken from https://ourworldindata.org/grapher/prevalence-cysticercosis) (right half-circles). We opted to use data on cysticercosis here, as it is a neglected tropical disease that is also transmitted locally in countries of the Global North, and hence not only a public health challenge in the Global South (Butala et al. 2021, Gonzalez-Alcaide et al. 2023).

Figures

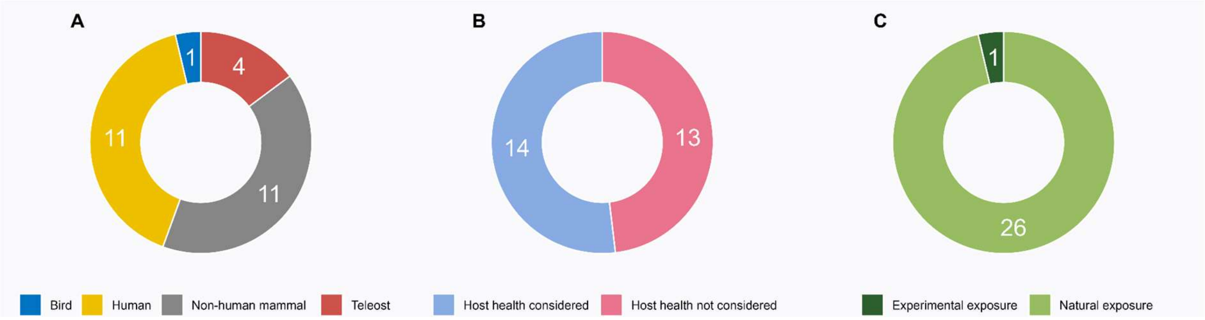

Figure 1

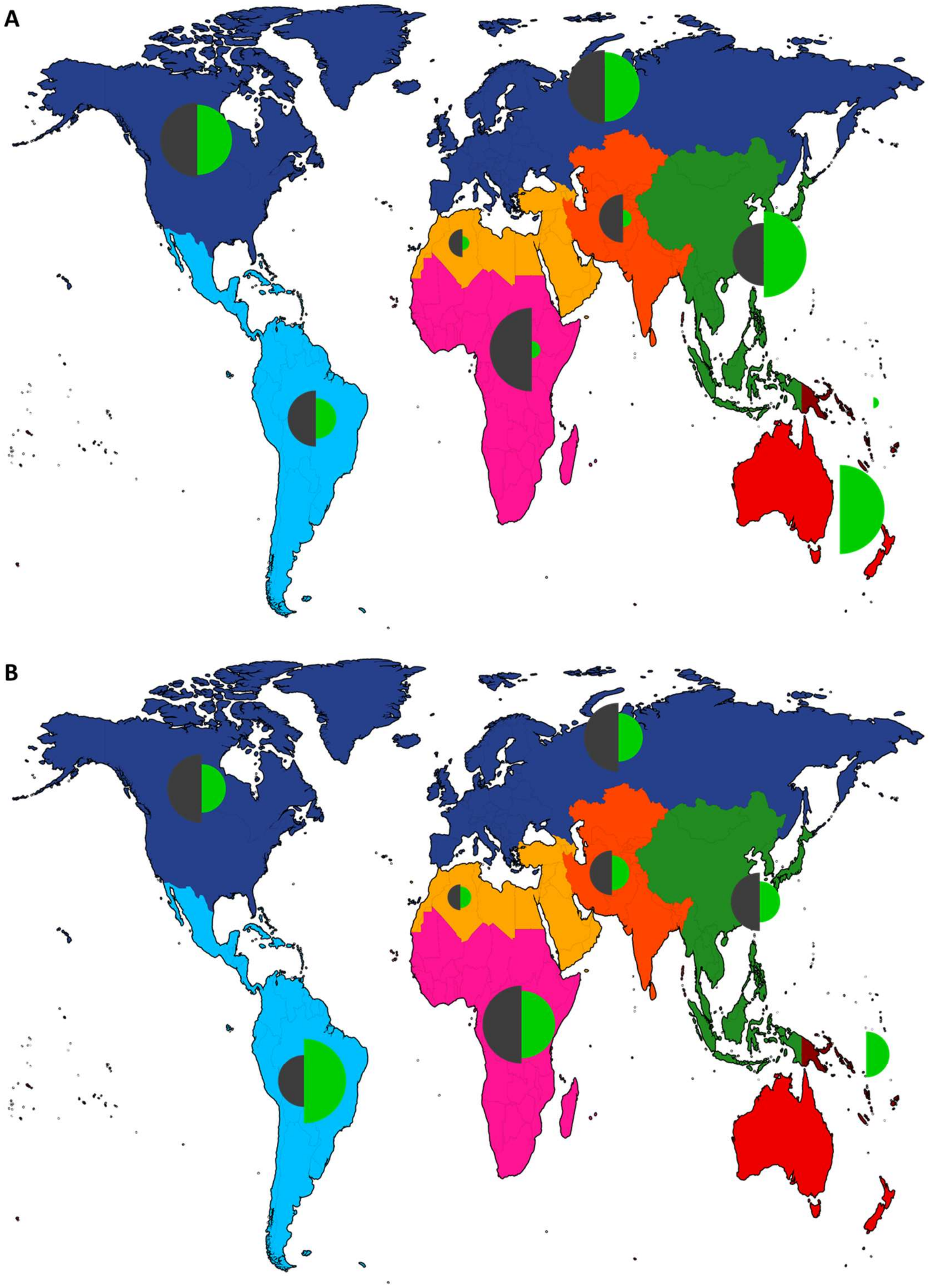

Figure 2