

**Title:** Treatment inefficacy for *Salmonella* during *Schistosoma-Salmonella* co-infections background, mechanisms and future exploration.

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## Abstract

Antibiotic inefficacy in treating bacterial infections is largely studied in the context of developing resistance mechanisms. However, little attention has been paid to combined diseases mechanisms, interspecies pathogenesis and the resulting impact on antimicrobial treatment. This review will consider the co-infections of *Salmonella* and *Schistosoma mansoni*. It summarises the protective mechanisms that the pathophysiology of the two infections confer, which leads to an antibiotic protection phenomenon. This review will elucidate the functional characteristics of the gut microbiota in the context of these co-infections, the pathogenicity of these infections in infected mice, and the efficacy of the antibiotics used in treatment of these co-infections over time. *Salmonella-Schistosoma* interactions and the mechanism for antibiotic protection are not well established. However, antimicrobial drug inefficacy is an existing phenomenon in these co-infections. The treatment of schistosomiasis to ensure the efficacy of antibiotic therapy for bacterial infections should be considered in co-infected patients.

**Keywords:** Co-infection, Drug resistance, Gut microbiota, Protective mechanism, *Salmonella*, Salmonellosis, *Schistosoma*, Schistosomiasis

## Introduction

The severity and treatment efficacy of schistosomiasis on bacterial, viral or other parasitic co-infections has a growing concern. Among the much studied are cases of *Salmonella* infection during schistosomiasis. Co-infections of *Schistosoma* and hepatitis B or C, malaria, leishmaniasis and HIV aslo are under study [1]. Moreover, *Schistosoma* as co-infection with other protozoa, with helminths and with bacteria other than *Salmonella* are also been studied [2]. Co-infections with *Schistosoma* and *Salmonella* confound the clinical picture of both diseases.

Evidence emerging from *in vitro* [3,4], animal model experiment [5] and clinical observations [6] regarding the symbiotic relationship existing between *Schistosoma* and *Salmonella* showed efficacy in the drug administered for treatment is only optimal when concurrent anti-Schistosomal therapy is administered. Although number of studies centred on the study of the concurrent *Schistosoma-Salmonella* infections, their complicated mechanisms where bacteria adhere to the adult Schistosomes present in the mesenteric vasculature require further research [3]. The pathogenicity of *Schistosoma mansoni*, alteration in host gut microbiota, and the evolution of drug resistance in concurrent *Schistosoma-Salmonella* infections *in vitro* and *in vivo* is yet to shed light on the pathogenicity of the two pathogens that might give rise to the evolution of antibacterial drug resistance [7]. To this end, the phenomena that give rise to persistent *Salmonella enterica* serovar Typhimurium bacteraemia or bacteriuria in the presences of *Schistosoma mansoni* will be explored in this review. The paper will investigate these synergistic effects of schistomiasis and salmonellosis as a co-infectoin.

## Salmonellosis as a disease

The most common bacterial genus causing foodborne infections is *Salmonella*. They infect wide range of hosts including human and bird species [8]. Worldwide, the various serovars of *Salmonella* spp. are known as a water and food borne gastrointestinal pathogens, and a systemic diseases pathogen. Typhoid fever alone is estimated at 10.9 million cases annually, most in low-

and middle-income countries [9]. In each year, 129.5 million cases of non-typhoidal *Salmonella* (NTS) human cases give between 100,000 and 1 million deaths worldwide [10]. With more than 2600 serovars, *Salmonella enterica* subspecies *enterica* infections are a persistent public health burden, among animals and food industry [11]. The pathogen is transmitted through contamination of food, water and fomites. Some serovars are species-specific but the vast number are "host-adapted" (broad host spectrum) serovars [11].

## Epidemiology

The genus *Salmonella* is divided into two species; *S. enterica* and *S. bongori*. *S. enterica* alone is further divided into 6 subspecies and more than 1500 serotypes. More than 99% of human salmonellosis is caused by *S. enterica* subspecies *enterica* [12]. Non-*enterica* subspecies of *Salmonella* have a reduced ability to invade host cells due to less essential virulence factors and thus are considered as opportunistic infections since they thrive well only in depressed host immunity [12].

## Invasive and non-invasive

There are more than 2600 serovars of *S. enterica* subsp. *enterica* and these are divided into typhoidal and NTS serovars. The two groups elicit diverse diseases and very distinct immune response in human host [13]. The *Salmonella enterica* serovars Typhi, Sendai and Paratyphi serotype A, B or C is human-restricted. These are called typhoidal *Salmonella* serovars as they cause the systemic diseases typhoid fever or paratyphoid fever, depending on pathogenic serovar [14]. Due to their invasiveness, infection with these serovars often leads to focal systemic infections and bacteraemia rather than gastroenteritis. Extra-intestinal non-typhoidal *Salmonella* (NTS) such as serovars Typhimurium, Dublin, and Choleraesuis causing invasive infections are also prominent [10] and invasive NTS is particularly in SSA [15].

As a major cause of global morbidity and mortality, non-typhoidal salmonella (NTS) invasive diseases comes second to Typhoid in case fatality [16] NTS serovars are associated with a high burden of foodborne *Salmonella* outbreaks in humans. These include the Typhimurium, Heidelberg, Newport and Enteritidis serovars [11]. Invasive NTS infections caused by *S. Typhimurium* and *S. Enteritidis* are the most prominent agents of invasive NTS disease. Naturally, these are generalist pathogens with broad host specificity. NTS induce gastroenteritis in 5% of

human cases [10]. Sickle-cell anaemic patients, those with recent malaria, adults with HIV infection and malnourished children are at higher risk [16].

## Pathogenicity

*Salmonella* pathogenicity Island 1, 2, 3, 4, and 5 (SPI-1, SPI-2, SPI-3, SPI-4 and SPI-5) are the collection of virulence factors that confer innate ability to cause diseases in both humans and animals. Inflammatory response due to the invasion of *Salmonella* into the gut-associated lymphoid tissues triggers inflammatory monocytes, macrophages, neutrophils, and dendritic cells. Toll-Like Receptor 11 (TLR11) induces inflammatory response. This activates TLR Signaling Pathway and triggers NF- $\kappa$ Bt activation [17]. *Salmonella enterica* has resilience factors that enable the serovars to resist gut antimicrobial peptides and bile [18]. The low pH of the stomach environment is not favourable to the vast number of microorganisms. However, in addition to acidic pH, antimicrobial peptides in the intestine, bile in stomach, *Salmonella* outcompete other commensal microbiota. Upon invading host cell, it dictates autophagy process and manipulates inflammatory pathways then eventually interacts with cells and T and B lymphocytes and evades the adaptive immune system [19]. *S. Typhimurium* may also initiate its own chemical signalling that regulates host hormonal metabolism. In doing so, they coordinate gene expression and hijack the competing microbial signalling in the gut [20]. Following series of signaling events, from innate to adaptive immunity, damage of intestinal wall is enhanced and the onset of invasion begins [17].

## Treatment options

*Salmonella enterica* serotypes Typhi and Paratyphi and Typhimurium may persist in the gut, causing ineffective antibiotic treatment and subsequently antimicrobial resistance [21]. Eradication and treatment of salmonellosis is becoming complicated by the emergence of multi-drug resistance (MDR) *Salmonella* spp. [22]. Increasing antibiotic-resistance in strains of *Salmonella* are an increasing infection, public health and economic burden in SSA [15]. In addition to the resistant strains, antibiotics disrupt the gut microbiota and the persisting antibiotic-induced diarrhoea promotes the reduction of benign bacterial population that produce the protective short chain fatty acids (SCFAs). SCFAs are required for various energy supplies such as colon cell proliferation and differentiation by Butyrate [23]. To curb this situation, alternative treatments

options are required. The supplementation of probiotic-organisms seems promising. However, the strain and organism type used as probiotic might encourage the growth of opportunistic pathogens. Furthermore, antibiotic susceptibility and antibiotic-resistant carriers are other phenomenal issues associated with probiotic complementary therapy. To this end, a holistic study on probiotic mechanisms and their efficacy is needed [24].

The current state in the treatment of salmonella infections does not look promising. Although the burden of infectious disease lies in the least developed countries, routine surveillance for antimicrobial resistance is not robust. For instance, NTS is now taken to be 50-70% MDR, including resistance to fluoroquinolones and 3rd generation cephalosporins. Furthermore, fluoroquinolones, which is the choice for MDR cases are not effective in treating *Salmonella Typhi* and *Salmonella Paratyphi A* [25]. Chloramphenicol, ampicillin and co-trimoxazole are also ineffective leaving quinolones as a choice to treat MDR *Salmonella* [26]. Kanamycin with an enhanced MDR *Salmonella* swarming properties on number of isolates is a promising treatment strategy [27].

Due to the poor economic status and inadequate resource in sub-Saharan Africa, the prudent use of effective antimicrobials looks unrealistic [25]. What this review will recommend is the typhoid vaccines and hope that there will be acceleration of trials for novel iNTS vaccines [25]. Again, a radical and aggressive approach is the only way to establish rational use of antibiotics during treating infections [26].

### **Issues in sub-Saharan Africa (sSA)**

*Salmonella* remains an important pathogen of humans and animals in low income countries globally [13]. The infections inflicted is serotype-specific [21]. Although not considered as a neglected tropical infection, *Salmonella* related deaths in 2010 were 129,000 out of the 11.9 million cases of typhoid fever across the globe. This is more than 100 cases per 100,000 person-years [28]. The more recent, 2 to 3 million cases of NTS gave a mortality rate of up to 700,000 deaths per year in sub-Saharan Africa. People who are immunocompromised are the much affected [10].

In SSA, gastroenteritis is the most common form of disease. The inflammatory response and toxins induced by bacterial overgrowth in intestinal submucosa and diarrhoea respectively are

the typical conditions [22]. As a leading cause of bacteremia in sSA, iNTS is has been representing a major public health burden. The two common iNTS serovars devastating children and immunocompromised individuals are *Salmonella* Typhimurium clade ST313 and *Salmonella* Enteritidis [29]. Taking Kenya as a case for sSA, iNTS has a mortality rate between 20-25% without prompt treatment strategy. Among the MDR isolates in one study conducted in Kenya, 8.5% are resistant to extended spectrum beta lactams. While asymptomatic carriage is concern for transmission especially among the vulnerable individuals, iNTS vaccine development could be seen as an emergency intervention [30].

### Schistosomiasis epidemiology

After malaria, Schistosomiasis is the parasitic diseases with the greatest impact socio-economic development more than 50 countries. These diseases are caused by trematodes of the genus *Schistosoma* [31]. Schistosomiasis is characterised as a neglected tropical disease by the World Health Organization (WHO) and poverty-related parasitic infection [32]. Schistosomes infect humans bathing fresh water and drinking untreated water in areas with inadequate sanitation facilities and the suitable watersnail intermediate hosts [33].

Six main species of schistosomes are established to cause diseases in humans. These are *Schistosoma mansoni*, *S. haematobium*, *S. intercalatum*, *S. guineensis*, *S. japonicum* and *S. mekongi*. While *S. haematobium* reside in the venous plexus of the bladder, leading to urinary schistosomiasis, the other human infecting species all reside in the venous plexus of the colon [33]. Human infections with hybrid strains of *S. haematobium* and *S. bovis* causing urinary schistosomiasis may be found in some parts of West Africa and the French island of Corsica [34,35]. The species of snails intermediate host vary, as does their geographical distribution [36]. *Biomphalaria* serve as hosts for *S. mansoni*, *Oncomelania* for *S. japonicum*, *Tricula* for *S. mekongi*, and *Bulinus* for *S. haematobium* and *S. intercalatum* [36]. In SSA, only *Schistosoma mansoni*, *S. haematobium*, *S. intercalatum* and *S. guineensis* cause human infections. *Schistosomiasis japonica* is a zoonosis in Asia with a water buffalo reservoir [37]

The risk factors associated with the occurrence of schistosomiasis are contact with water that harbours the intermediate host snail. Also, the level of education, sex, age and the family income determine the incidence of schistosomiasis. In essence both environmental and social conditions influence this condition [38]. Poor socio-economic status, unhygienic recreational swimming and environmental degradation due to urbanization promote the endemicity of the diseases [39]. The associating factor that influences the pathophysiological mechanism of schistosomiasis is blood group type. Even though not enough studies have gathered evidence, blood group type B and A are more susceptible to schistosomiasis than those who are blood type O [40].

### ***Schistosoma* life cycle**

In contaminated water, the parasitic helminths Schistosomes infect humans through dermo-invasion. After the migration of schistosomulae to the lung, the adult worms reside in blood vessels in a close proximity of intestinal mucosa [41]. Through asexual or sexually reproduction, the life of schistosome snails and mammals host. In sexual reproduction, it occurs in freshwater snails. This begins with the development of miracidia into a sporocyst and these sporocysts will then multiply and grow into cercariae. For the mammalian hosts like humans, mice, and dogs, the parasites grow, mature, mate, and produce eggs [42].

### **Schistosomiasis disease**

It is estimated that, 230 million people from the 74 developing tropical and subtropical countries are infected by schistosomiasis yearly. 200,000 deaths are recorded per year [43]. Furthermore, there are number of asymptomatic cases and those with the appearance of symptoms. Asymptomatic infections represent approximately 16.7% of the 120 million affected persons [43].

In human, the clinical manifestations of schistosomiasis are in three phase and these are; acute, sub acute and chronic stages. Once the matured parasite settled in the targeted organs, for example, in the lower urinary tract with *Schistosoma haematobium* and the other species in colon and rectum, it develop into secondary manifestations, which happens in liver, lungs, kidneys etc. The healing of granulomata by fibrosis and calcification in the renal glomeruli by deposition of



schistosomal antigen-antibody complexes, the development of secondary amyloidosis or at the sites of oval entrapment are attributed to chronic morbidity [1].

Based on the immune response, the clinical manifestations of schistosomiasis fall under acute, sub-acute and chronic stages. The acute stage (Katayama fever) is species-specific and is seen during the early invasion and migration [44]. During the log phase of parasite growth curve, granulomata around the eggs are formed.

Immunity is seen during the chronic stages of disease. During this stage, the pathogen will gain an upper hand against innate, TH1 and TH2 adaptive cells [1]. Complications are seen among some patients. Co-infections or associated pathogenic agents will persist and this condition affects salmonella disease treatment efficacy [2]. Inflammation, liver fibrosis, micro abscess formation, ulceration, polyposis and hyperplasia are abnormal physiological functions induced by *Schistosoma* ova [33].

### **Pathogenicity**

Schistosome eggs will have to pass through the intestinal wall without inflicting enteric inflammation. Some eggs reach ectopic sites such as the kidney, liver, genitourinary tract and central nervous system. Immune response from the host due to proteolytic enzymes produced by those retained eggs results in eosinophilic inflammation and granuloma formation [45]. The pathogenicity is proven difficult to control during the secondary manifestations. These manifestations occur in organs such as liver, kidneys, lungs and other ectopic sites [2].

Deposition of *Schistosomal* antigen-antibody complexes in the renal glomeruli are attributes of chronic morbidity. In addition, the development of secondary amyloidosis, the healing of granulomata by fibrosis, co-infection with hepatitis C [44] and calcification at the sites of oval entrapment are seen during chronic morbidity [2]. Pelvic venous plexus is a virulence factor that can enable male and female worms to co-habit for several decades. This protects the worms from host immune invasion [44]. In the study of bladder cancer in Africa, the pathogenesis of squamous cell carcinoma (SCC) is *S. haematobium*-related [46].

## Prevention and Treatment

The preventive measures for schistosomiasis will not be effective without effective education and periodic mass treatment. The implementation of chemical mollusciciding-based control of *Bulinus* and *Biomphalaria* spp., snails is proven effective. With the elimination of these intermediate hosts, local transmission is drastically reduced, albeit incomplete. *S. mansoni* and *S. haematobium* transmission are minimized even in the in high risk areas [47].

Praziquantel as the drug of choice has 80% cure rate and can only be supplemented with effective vaccine for absolute eradication of schistosomiasis [2]. However, for fibrotic lesions, surgical treatment is the last resort. In effective reduction of infection intensity, Praziquantel 40 mg/kg is recommended among preschool- and school-aged children [48].

To elicit a mucosal response, attenuated *S. Typhimurium* strain (YS1646) is produce as multi-modality vaccine. This intervention is targeting Cathepsin B (CatB) is a promising intervention for complete protection against *S. mansoni* [41]. *Schistosoma* vaccine development is promised on oral delivery of the antigen by nirB-driven *S. Typhimurium* type III secretion system [49].

## *Schistosoma* and *Salmonella* co-infections

Dual *Schistosoma* and *Salmonella* infection is a public health challenge and other schistosomiasis endemics. The interactions of *Schistosoma* and *Salmonella* is favored by the immunosuppression of the host due parasitic infections [50]. As both are water-borne human pathogens common in areas with poor sanitation, the co-existence of *Schistosomes* and *Salmonella* infections is a common occurrence.

The type of organisms involved, order and time of interval between the infections, the pedigrees of the parasites, infectious agents are all associating factors that appear to determine the synergistic pathogenicity of the co-infection [51]. Another confounding factor in the study of *Schistosoma* co-infection is the prior infection with *Schistosoma*, which has effects on the subsequent infection. With this prior infection, the severity of subsequent infection with *Fasciola hepatica*, *Plasmodium*, *Echinostoma* or *Helicobacter pylori* is decreased [51]. In contrast to

*Toxoplasma gondii*, *Leishmania*, *Staphylococcus aureus*, *Entamoeba histolytica* or *Salmonella*, the subsequent infection appear to present in a more severe form with a prior infection with *Schistosoma* [51]. Co-infection is projected to be increasingly associated with the prevalence uncomplicated *P. falciparum* infection in children. However, an interesting reduction of haemoglobin level in high density *P. falciparum* infection was observed [52].

### Medical Importance of co-infections

The incidence of high morbidity and mortality of helminth infections come with intracellular pathogens such as *Salmonella*. Prolonged fever and enlarged liver and spleen are some clinical manifestation associated with co-infections, in addition to chronic septicemic salmonellosis. These are seen with patients with *Salmonella-Schistosoma* co-infections [53]. Conversely, complicated persistent *Salmonella* urinary tract infection was found to be associated with urinary schistosomiasis [53]. *Schistosoma-Salmonella* co infections lead a chronic septicemic salmonellosis. In addition to higher bacterial load, this co-infection will first impair IFN- $\gamma$  and IL-17 responses. This is facilitated via basophils recruitment by a glycoprotein secreted live schistosome eggs (IPSE/ $\alpha$ -1) . IPSE/ $\alpha$ -1 will trigger IL-4 and IL-13 release from basophils and the overall immunoregulatory activities are studied to give a prolong fever and enlargement of liver and spleen [21].

### Pathogenicity of co-infection

The co-infection of *Schistosoma* with *S. Typhimurium* can ameliorate schistosomiasis in the metabolic alterations associated with infection since the host immune response is manipulated by the secondary bacterial infection [6]. *Salmonella* can evade the effects of antibiotics via adherence to *Schistosomes*. (Table 1). *Salmonella* can attach to the outer cuticle of adult schistosomes. In this state, are resistant to antibiotics via a protective mechanism [54]. The protective mechanism and proven treatment inefficiency is hypothesized to be the overall immunoregulatory activities of *Schistosomes*. These activities include induction of Tregs, Bregs degrades antibodies and alternatively activated macrophages [21]. *In vitro* design of study to qualitatively assess some common antibiotics has gathered evidence regarding *Salmonella* adhering to schistosomes.

Study design	Significant findings	Conclusion
Intraperitoneal application of live <i>S. mansoni</i> eggs prior to infection with <i>S. Typhimurium</i> [21].	An impairment of IFN- $\gamma$ and IL-17 responses together with a higher bacterial load compared to <i>Salmonella</i> infection alone. IPSE/alpha-1 is known to trigger IL-4 and IL-13 release from basophils, which in turn is known to suppress Th1/Th17 responses.	That <i>S. mansoni</i> infection impairs a protective immune response against <i>Salmonella</i> infection is supported by the data.
Evaluation of <i>Schistosoma</i> -mediated protection of <i>Salmonella</i> Typhimurium strain SL1344 from other antibiotics in flatworm [13]	A reduction in efficacy of antibiotics due to the association of schistosomes and <i>Salmonella</i> . Insignificant elevation in the antibiotic resistance when the non-invasive isostrain and hyperinvasive isostrain were recalcitrant to the antibiotics.	The protection mechanism might not be related to invading the tegument cells of <i>Schistosomes</i> . It is related to the glycocalyx of <i>Schistosoma</i> integral milieu. Instead, fimbrial protein (FimH) found in the surface of the bacterium is the feature conferring abilities for <i>Salmonella</i> to bind and seek protection from antibiotics.
Dual infections of enteric <i>Salmonella</i> Paratyphi A with <i>S. mansoni</i> among Patients [55]	<i>Salmonella</i> Paratyphi is resistant to antibiotic treatment when in co-infection with <i>S. mansoni</i> .	The virulent factor might be the bearing of cell surface epitope that is analogous to the mammalian cell-

		docking site for FimH protein
Elucidating rheumatoid factors in <i>Salmonella</i> and <i>Schistosoma</i> infections [56]	<p>Titres of rheumatoid factor decreased. 2-mercaptoethanol was consistently eliminated.</p> <p>Similar complete elimination of <i>Salmonella</i> somatic antigen agglutinins was observed in sera of some patients with either chronic or acute <i>Salmonella</i> infection.</p>	<p>Completely the titres of rheumatoid factors, indicating that all were probably IgM.</p> <p>Similar results in acute typhoid and paratyphoid fevers deem further study on the pathogenesis of IgM anti-globulin antibodies associated with infections.</p>
NMR-based metabonomics and immunological techniques for the systemic metabolic and immune responses using a mouse model of co-infection [57].	<p><i>S. Typhimurium</i> (ATCC14028) infection reduced the number of adult <i>S. japonicum</i> adults and eggs, relieved symptoms of schistosomiasis and also abated the mortality of mice infected by <i>S. japonicum</i>.</p> <p><i>S. Typhimurium</i> co-infection counteracted the metabolic disturbances associated with schistosomiasis, which was reflected by the reverted levels of metabolites in co-infected mice.</p> <p>Shift of the immune response to different pathogens is a result of indirect interactions between <i>S. japonicum</i> and <i>S. Typhimurium</i> within the host.</p>	<p><i>S. Typhimurium</i> infection can ameliorate <i>S. japonicum</i>-induced schistosomiasis in BALB/c mice.</p> <p>This is most likely due to inverse immune polarization.</p>

To elucidate the mechanism(s) of the parasite-parasite interaction of <i>S. Typhimurium</i> LT2 on the surface of <i>Schistosoma mansoni</i> , <i>S. haematobium</i> and <i>S. japonicum</i> [58].	100% association of the ga/E and fla mutants with male schistosomes, but a reduced interaction with female worms. Reduction in the rough A and pil mutants' ability to associate with both male and female <i>S. mansoni</i> . Pili function in adhesion of <i>Salmonella</i> to the surface tegument of <i>S. mansoni</i> and <i>S. haematobium</i> .	Persistence of <i>Salmonella</i> infection may due to the association with <i>Salmonella</i> spp.
<i>Salmonella</i> Typhimurium and Enteritidis intestinal carriage and <i>S. mansoni</i> infection using multi-locus variable-numbers tandem repeat analysis (MLVA) [6].	The proportion of <i>Salmonella</i> carriage is higher among <i>S. mansoni</i> infected participants and even higher in those showing fever.	<i>Salmonella</i> intestinal carriage was associated with a heavy intensity of <i>S. mansoni</i> infection.
Intraperitoneally, <i>S. t</i> =Typhimurium ATCC14028 is inoculated into mice harbouring different developmental stages of <i>S. mansoni</i> [59].	The growth of Schistosomes alone is more significant ( $p<0.05$ ) when compared to <i>S. Typhi</i> culture in co-infection with <i>Schistosoma</i> -infected mice. The growth is more confluent in older <i>Schistosomes</i> .	Adult schistosomes, not young worms modified responses to treatment of mice with <i>Salmonella</i> infection in concurrent infection.
Pilus-negative and a pilus-producing transductant strain of <i>S.</i>	The association of <i>S. Typhimurium</i> to the surface tegument of <i>Schistosoma</i> Mechanism of interaction of	Pili are the ligands for bacterial adherence to

Typhimurium in an <i>in vitro</i> system [3]	<i>Salmonella</i> and <i>Schistosoma mansoni</i> was blocked.  The <i>Schistosoma</i> helminths provide a multiplication focus for these bacteria in the portal mesenteric system, with a persisting bacteremia.	the schistosome surface tegument.  Prolonged salmonellosis in <i>Schistosoma</i> -infected patients is due to an association of <i>Salmonella</i> spp. with the <i>Schistosoma</i> worms themselves.
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## The effects of antibiotic treatment on co infection

### Antibiotic Protection

In a bid to treat patients infected with Schistosomiasis, anthelmintic praziquantel (PZQ) is a common therapeutic drug. However, dysbiosis seems an effect associate with this intervention. A shift in gut microbiota composition pre and post PZQ treatments was seen [60]. Although the gut bacterial population varies between people infected with schistosomiasis and those who do not, the abundance phyla were *Bacteroides*, then *Firmicutes* and *Proteobacteria* between the pre and post-treatment [61]. Furthermore, only limited variations in the relative abundance of taxa among bacterial classes and this variation is not affiliated to age or sex of the participants.

### Antibiotic Concentration against bacteria

As a result of *Schistosoma*-associated *Salmonella*, the adherence of bacteria to the flatworm reduces the efficacy of antibiotic treatments targeting those *Salmonella*. The concentrations of the antibiotic used during the *in vitro* antibiotic assay assessment against *Salmonella-Schistosoma* co-infection were studied to effect killing bacteria at a relative rate. Using a novel antibiotic protection assay, an absolute (100%) efficacy of ANTIBIOTIC (amoxicillin (32 µg/ml), cefepime (32 µg/ml), cefpodoxime (32 µg/ml), chloramphenicol (32 µg/ml), ciprofloxacin

(4 µg/ml), streptomycin (32 µg/ml), sulfadimethoxine (512 µg/ml), or tetracycline (16 µg/ml) was seen with *Salmonella* strains incubated alone, while a decreased efficacy of less than 12% of the same strains when incubated with adult *Schistosoma mansoni* [13]. This protective mechanism is in contrast to the hypothesis that arises on the basis of the virulent nature of the strain type of *Salmonella*. Specific fimbrial protein (FimH) present on the surface on the bacterium confers binding to Schistosomes. When both invasive strains and non-invasive strains of *Salmonella typhimurium* were incubated with *Schistosomes mansoni* under the same amoxicillin concentration (32 µg/ml), the protective mechanism against the effects of amoxicillin enables the bacteria to live. Based on concentration on co-incubation with the control free-living flatworm *Girardia tigrina* and with Hep-2 mammalian tissue culture cells showed no replication of this protective mechanism. Unlike *Salmonella* spp., *Escherichia coli* did not benefit from the protective mechanism of attachment to schistosomes[13]. In order to achieve therapeutic levels or treatment efficiency of the antibiotic used in co-infections study, perturbing the binding mechanism to schistosomes is required to eliminate *Salmonella* [13].

### **Antimicrobial treatment failure due to co-infections**

It is ascertained that any ineffective use of antibiotics may result in resistance gene acquisition and expression [13]. *Salmonella* factors facilitate the attachment to *Schistosoma* and they catalogued the antibiotics that are infective against the co-infection [13].

*Schistosoma-Salmonella* co-infections are as a result of the enteroinvasive *Salmonella* entering the systemic circulation whereby the *Salmonella* attach to the tegument of adult *Schistosoma* in the mesenteric vasculature [4, 5, 62]. In a normal *Schistosoma* infected patient, the anthelmintic praziquantel is a key choice of therapy. However, in cases of *Schistosoma*-associated *Salmonella*, such therapy is observed to cause a massive release of *Schistosoma*-associated *Salmonella*, leading to acute septicaemia among children when *Salmonella* treatment options are not co-administered [63, 64].

### ***Salmonella* interactions with the microbiome**

*Salmonella* infection in a mouse model has been seen to drastically alter the homeostasis of gut microbiota and thus the intestinal metabolome. The physiological functions and hormone metabolism were significantly altered [65]. *S. Typhimurium* is a prominent competitor with



commensal gut microbiota. Once they dominate the gut microbiota population, their invasion signals the onset of infection.

Both intestinal and urinary schistosomiasis will also alters the gut microbiome (Table 2).

Study methodology	Effects on gut microbiota	Study Conclusion
NMR-based metabonomics and immunological techniques to detect systemic metabolic and immune responses of <i>Schistosoma japonicum</i> and <i>S. Typhimurium</i> (ATCC14028) coinfection in BALB/c mice [57].	<i>S. Typhimurium</i> infection reduces the number of adult schistosomal worms and eggs. Due to inverse immune polarization, <i>S. Typhimurium</i> infection can ameliorate <i>Schistosoma japonicum</i> -caused schistosomiasis and counteracts the metabolic disturbances associated with schistosomiasis	The study found some insight into the development of new tools for controlling <i>Schistosoma japonicum</i> -associated diseases.
Shotgun metagenomic sequencing used to characterise the gut microbiome and resistome of Zimbabwean preschool-aged children (1-5 years). [46].	Bacteria phyla <i>Bacteroidetes</i> , <i>Firmicutes</i> , <i>Proteobacteria</i> , and fungi phyla <i>Ascomycota</i> , <i>Microsporidia</i> , <i>Zoopagomycota</i> dominate the microbiome. Specifically, infection is associated with increases in <i>Pseudomonas</i> , <i>Stenotrophomonas</i> , <i>Derxia</i> , <i>Thalassospira</i> , <i>Aspergillus</i> , <i>Tricholoma</i> , and <i>Periglandula</i> , with a decrease in <i>Azospirillum</i>	A novel metagenomic dataset that indicates an association between urogenital schistosome infection and changes in the gut microbiome.
Screening the gut microbiota of <i>S. mansoni</i>	Over-abundance of <i>Fusobacterium</i> spp. in cured	Dysbacteriosis of the gut microbiota was not

<p>infected and uninfected children from Côte d'Ivoire using V3 and V4 regions of 16S rRNA genes.</p> <p>Follow-up on samples after administering 60 mg/kg praziquantel or placebo [66]</p>	<p>children. No significant effect on the microbial composition.</p>	<p>induced by <i>S. mansoni</i> and a specific microbiome profile could not influence praziquantel response.</p>
<p>Assessing the influence of gut microbiota in the 28 kDa glutathione S-transferase (P28GST; a schistosome derived enzyme)-mediated anti-inflammatory effects of mice faecal microbiota transplantation.</p> <p>The experimental data were supplemented by the temporal fecal microbiota compositions of P28GST-treated Crohn's disease patients from a pilot clinical study [67].</p>	<p>The P28GST slightly modulated the diversity and composition of mouse fecal microbiota.</p> <p>However, colitis is significantly reduced in experimental mice.</p>	<p>This study opens the door to helminth-derived molecules, as promising safe therapeutic use of immunomodulation</p>
<p>Liquid chromatography tandem mass spectrometry (LC-MS/MS) platform for comparison between the metabolic profiles of the male and female <i>S. japonicum</i> worms collected from SCID mice and</p>	<p>There is an association between the schistosome with retarded growth and development in SCID mice.</p> <p>Their perturbed metabolites and metabolic pathways provided a new insight into the growth and</p>	<p>This study gives great clues for discovery of drugs or vaccines against the parasites and disease.</p>

BALB/c mice at 5 weeks post infection [68].	development regulation of <i>S. japonicum</i> worms. At metabolic level, this indicated great clues for discovery of drugs or vaccines against the parasites and disease with more researches.	
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### Microbiome and co-infection

Commensal microorganisms called gut microbiota are vast number of organism living gastrointestinal (GI) tract of vertebrates. Their functions range from maintenance of energy balance, nutrition and host immunity [69], and the production of antimicrobial products, bacteriophages deployment and enhancing gut barrier integrity [70]. A healthy gut microbiome is a critical defence against colonization of pathogenic or exogenous microorganisms. This effect is referred to as colonization resistance (CR) and helps to minimize exogenous pathogens, which many colonize the gut and ultimately cause infection [65]. An imbalance of these dysbiosis is associated with number of chronic and autoimmune disorders. Besides environmental factors, macrobiota including parasitic helminths with their pathogenic effects including metabolic activity, immune system and lead to infection [65]

Of recent, the role of gut microbiome is shedding more lights to health of host and the functions not limited to are the biochemical, immunological and nutritional response of the gut microbiome are more a less biomarkers [68]. To add scholarly evidence to the existing and emerging theories, this review will create literature for a further study to investigate the role of the gut microbiome in parasitic infection, co-infections, and the antibiotic resistance due to the pathology. The acquired immunity among patients when exposed to helminths, aggravated with bacterial infections and the resulting immune response to the concurrent infections [71]. In a bid to assess the impact of sequential infection of bacteria and helminths on the host, this reviewisvowed to consider the co infection of *S. Typhimurium* and *S. mansoni*.

### Metabolic response to the co-infection

Metabolomics has been a robust tool in studying metabolic response to series of stimuli and one such is a co-infection [72]. Chromatography coupled to mass spectrometry or <sup>1</sup>H nuclear magnetic resonance (NMR) spectroscopy, with the multivariate statistical analysis aid to determine metabolic changes in system response to stress or stimuli [73]. Alternative therapeutic such as personalized medicine based on microbiome might get its roots from the effects of *Salmonella* in the co-infection provided that, the salmonella serotype is non-invasive and non-pathogenic.

Using the NMR-based Metabolomics and immunological techniques to detect the systemic metabolic and immune responses, respectively, this study concluded *Salmonella enterica* serovar Typhimurium effects reduction in egg counts and the number of adult worms and relieves symptoms of schistosomiasis [57]. The metabolic disturbance of co-infected mice was compared with *S. japonicum*, reverted levels of metabolites result from the former infection. Due to inverse immune polarization; the bacteria have been seen to ameliorate *S. japonicum* induced schistosomiasis in BALB/c mice [57]. In order to explore on this pathogenicity, other forms of *Schistosoma* should be studied in co-infection with the same serotype of *Salmonella*.

### **Immune response to the co-infection**

A shift in host immune response from Th1 to Th2 polarization is studied to be an effect of *Schistosoma* infection of a typical schistosomiasis [57]. The alteration is achieved due to the progress of the disease including cercariae intrusion, migration of larvae, pairing in adult and laying of eggs [74]. Unlike *Schistosoma*, infection caused by *S. Typhimurium* only induces Th1 polarization [75].

The clinical significance of the host immune impairment by the combined effects of the *S. Typhimurium* and *S. mansoni* could draw much attention to the interaction between these two species. One instance is the influence of gut microbiota on the generation of Th17 cells. The effector lineage of CD4 T cells with protective abilities against inflammatory and harmful autoimmune conditions are Th17 cells. They mobilize host immunity against microbial pathogens such as *Salmonella* [76]. Expansion of segmented filamentous bacteria (SFB) is also inhibited with an increase in  $\alpha$ -defensin expression of IL-17. Low number of IL-17-producing Th17 cells in the lamina propria signals loss of  $\alpha$ -defensin and expansion of SFB [77]. While much attention is paid on bacterial benefits to the host immunity, benign worms and viral species are yet to be explored.

## Future Research

*Salmonella* resistant to multiple antimicrobials worldwide is a threat to global health. The emerging of clones of resistant strains even in the under developed world requires a holistic approach on food chain and distribution system [78]. An improved understanding of the impact of genome variation of bacterial pathogens on pathogen-host and pathogen-environment interactions has the potential to improve quantitative risk assessment and reveal how new pathogens evolve [10]. The physical barrier theory of mammalian cell-docking site for FimH protein [55], begs for a further study despite it is ascertained that the resistance is transient and is observed only during adherence.

The efficacy of antibiotics will be determined by the weekly faecal culture for bacteria responsible for urinary tract infections and stomach disorders. Such study is hoped to ascertain the body's immune response to *S.mansoni* infection in co-infection. This will be based on the granulomatous reaction involving T cells, macrophages, and eosinophil of group of antibiotic and non-antibiotic interventions and on the *Schistosoma* weekly egg counts through time. With respect to *in vitro* study, novel antibiotic protection assay of antibiotic-sensitive, *Salmonella* strains are ought to be developed, incubated with a known concentration of effective therapeutic proven antibiotic. In sense, the lethal dose should be 100% effective to eliminate *Salmonella* strains in the void of concurrent *Salmonella* infections [3].

The study of co-infections involving *Schistosoma* and *Salmonella* should be based on model that will explain a wholesome range of parameters. Study of the mucosal cell gene expression, innate and adaptive mucosal immune responses, the virulence expressed by the pathogens involved, microbiota gene expression and the genetic profiling of the host will confer clear explanation to the homeostasis [69].

## Conclusion

In a bid to curb with the emerging infectious diseases in Sub-saharan Africa, much paid attention should be equally paid to the treatment inefficacy arising as a result of co-infection. These combined disease mechanism has ways to escaope antimicrobial treatment. We dwelled on co-infections of *Salmonella* and *S. mansoni* to ascertain the antibiotic protection phenomenon and functional characteristics of the gut microbiota.

*Salmonella-Schistosoma* co-infections need more study to decipher on the exact phenomenon existing with regards to the pathogenicity. Establishing the protective mechanism conferred by schistosomes for *Salmonella* to survive antibiotic treatment are still not clear as per mechanism.

## **Declarations**

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

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## **References**

- 1) Barsoum RS, Esmat G, El-Baz T. Human schistosomiasis: clinical perspective: review. *J Adv Res.* 2013;4(5):433-444
- 2) Abruzzi A, Fried B. Coinfection of *Schistosoma* (Trematoda) with bacteria, protozoa and helminths *AdvParasitol.* 2011;77:1-85
- 3) Melhem RF, LoVerde PT. Mechanism of interaction of *Salmonella* and *Schistosoma* species. *Infect Immun.* 1984; 44(2):274-281.
- 4) Gendrel D, Kombila M, Beaudoin-Leblevec G, Richard-Lenoble D. Nontyphoidal salmonellal septicemia in Gabonese children infected with *Schistosoma intercalatum*. *Clin Infect Dis.* 1994; 18(1):103-105.
- 5) Wilson R, Elthon J, Clegg S, Jones B: *Salmonella enteric* serovars *gallinarum* and *pullorum* expressing *Salmonella enterica* serovar *typhimurium* type 1 fimbriae exhibit increased invasiveness for mammalian cells. *Infect Immun.* 2000, 63: 4782-4785.
- 6) Mbuyi-Kalonji L, Barbé B, Nkoki G, et al. Non-typhoidal *Salmonella* intestinal carriage in a *Schistosoma mansoni* endemic community in a rural area of the Democratic Republic of Congo. *PLoS Negl Trop Dis.* 2020;14(2):e0007875
- 7) Keren I, Shah D, Spoering A, Kaldalu N, Lewis K: Specialized persister cells and the mechanism of multidrug tolerance in *Escherichia coli*. *J Bacteriol.* 2004, 186: 8172-8180.
- 8) Jajere SM. A review of *Salmonella enterica* with particular focus on the pathogenicity and virulence factors, host specificity and antimicrobial resistance including multidrug resistance. *Vet World.* 2019;12(4):504-521
- 9) Birkhold M, Coulibaly Y, Coulibaly O, Dembélé P, Kim DS, Sow S, Neuzil KM. Morbidity and Mortality of Typhoid Intestinal Perforation Among Children in Sub-Saharan Africa 1995-2019: A Scoping Review. *World J Surg.* 2020 Sep;44(9):2892-2902.
- 10) Birkhold M, Coulibaly Y, Coulibaly O, Dembélé P, Kim DS, Sow S, Neuzil KM. Morbidity and Mortality of Typhoid Intestinal Perforation Among Children in Sub-Saharan Africa 1995-2019: A Scoping Review. *World J Surg.* 2020 Sep;44(9):2892-2902.
- 11) Jajere SM. A review of *Salmonella enterica* with particular focus on the pathogenicity and virulence factors, host specificity and antimicrobial resistance including multidrug resistance. *Vet World.* 2019;12(4):504-521
- 12) Lamas A, Miranda JM, Regal P, Vázquez B, Franco CM, Cepeda A. A comprehensive review of non-enterica subspecies of *Salmonella enterica*. *Microbiol Res.* 2018; 206:60-73.

- 13) Barnhill AE, Novozhilova E, Day TA, Carlson SA. *Schistosoma*-associated *Salmonella* resist antibiotics via specific fimbrial attachments to the flatworm. *Parasit Vectors*. 2011; 4:123.
- 14) Gal-Mor O, Boyle EC, Grassl GA. Same species, different diseases: how and why typhoidal and non-typhoidal *Salmonella enterica* serovars differ. *Front Microbiol*. 2014;5:391.
- 15) Saffiatou Darboe, Richard S. Bradbury, Jody Phelan, Abdoulie Kante, Abdul-Khalie Muhammad, Shangxin Yang, Blanca Perez-Sepulveda, Jay C.D Hinton, Davis Nwakanma, Samuel Kariuki, Martin Antonio\* and Brenda Kwambana-Adams. 2021. Non-typhoidal *Salmonella* (NTS), invasive NTS (iNTS), *Salmonella* Typhimurium, *Salmonella* Enteritidis, West Africa. *Under review*.
- 16) GBD 2017 Non-Typhoidal *Salmonella* Invasive Disease Collaborators. The global burden of non-typhoidal salmonella invasive disease: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis*. 2019; 19(12):1312-1324
- 17) Guiney DG. The role of host cell death in *Salmonella* infections. *Curr Top Microbiol Immunol*. 2005;289:131-150
- 18) Schultz BM, Paduro CA, Salazar GA, et al. A Potential Role of *Salmonella* Infection in the Onset of Inflammatory Bowel Diseases. *Front Immunol*. 2017;8:191
- 19) Bernal-Bayard J, Ramos-Morales F. Molecular Mechanisms Used by *Salmonella* to Evade the Immune System. *Curr Issues Mol Biol*. 2018;25:133-168
- 20) Gart EV, Suchodolski JS, Welsh TH Jr, Alaniz RC, Randel RD, Lawhon SD. *Salmonella* Typhimurium and Multidirectional Communication in the Gut. *Front Microbiol*. 2016;7:1827
- 21) Schramm G, Suwandi A, Galeev A, et al. Schistosome Eggs Impair Protective Th1/Th17 Immune Responses Against *Salmonella* Infection. *Front Immunol*. 2018; 9:2614.
- 22) Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive *Salmonella* disease. *Vaccine*. 2015;33 Suppl 3(0 3):C21-9.
- 23) Akhtar S, Sarker MR, Jabeen K, Sattar A, Qamar A, Fasih N. Antimicrobial resistance in *Salmonella enterica* serovar typhi and paratyphi in South Asia-current status, issues and prospects. *Crit Rev Microbiol*. 2015;41(4):536-45.
- 24) Brunelle BW, Bearson BL, Bearson SMD, Casey TA. Multidrug-Resistant *Salmonella enterica* Serovar Typhimurium Isolates Are Resistant to Antibiotics That Influence Their Swimming and Swarming Motility. *mSphere*. 2017 ;2(6):e00306-17.



- 25) Smith SI, Seriki A, Ajayi A. Typhoidal and non-typhoidal *Salmonella* infections in Africa. *Eur J Clin Microbiol Infect Dis*. 2016;35(12):1913-1922
- 26) Guarner, F. and J.R. Malagelada, Gut flora in health and disease. *Lancet*, 2003. 361(9356): p. 512-9
- 27) Gut AM, Vasiljevic T, Yeager T, Donkor ON. *Salmonella* infection - prevention and treatment by antibiotics and probiotic yeasts: a review. *Microbiology (Reading)*. 2018; 164(11):1327-1344.
- 28) Hsiao A, Toy T, Seo HJ, Marks F. Interaction between *Salmonella* and Schistosomiasis: A Review. *PLoS Pathog*. 2016;12(12):e1005928
- 29) Piccini G, Montomoli E. Pathogenic signature of invasive non-typhoidal *Salmonella* in Africa: implications for vaccine development. *Hum Vaccin Immunother*. 2020; 16(9):2056-2071.
- 30) Kariuki S, Mbae C, Van Puyvelde S, Onsare R, Kawai S, et al. High relatedness of invasive multi-drug resistant non-typhoidal *Salmonella* genotypes among patients and asymptomatic carriers in endemic informal settlements in Kenya. *PLoS Negl Trop Dis*. 2020;14(8):e0008440
- 31) Xu J, Bergquist R, Qian YJ, et al. China-Africa and China-Asia Collaboration on Schistosomiasis Control: A SWOT Analysis. *Adv Parasitol*. 2016; 92:435-466.
- 32) Madinga J, Linsuke S, Mpabanzi L, et al. Schistosomiasis in the Democratic Republic of Congo: a literature review. *Parasit Vectors*. 2015;8:601
- 33) Haeusler GM, Curtis N. Non-typhoidal *salmonella* in children: Microbiology, epidemiology and treatment. *Adv Exp Med Biol*. 2013; 764.
- 34) Webster BL, Diaw OT, Seye MM, Webster JP, Rollinson D. Introgressive hybridization of *Schistosoma haematobium* group species in Senegal: species barrier break down between ruminant and human schistosomes. *PLoS Negl Trop Dis*. 2013;7(4):e2110.
- 35) Boissier J, Grech-Angelini S, Webster BL, Allienne JF, Huyse T, Mas-Coma S, Toulza E, Barré-Cardi H, Rollinson D, Kincaid-Smith J, Oleaga A. Outbreak of urogenital schistosomiasis in Corsica (France): an epidemiological case study. *The Lancet Infectious Diseases*. 2016;16(8):971-9.
- 36) Pearce E.J. (2005) The Initiation of Host Immune Responses to Schistosome Egg Antigens. In: Secor W.E., Colley D.G. (eds) Schistosomiasis. World Class Parasites, vol 10. Springer, Boston, MA. [https://doi.org/10.1007/0-387-23362-8\\_8](https://doi.org/10.1007/0-387-23362-8_8)
- 37) Gray DJ, Williams GM, Li Y, McManus DP. Transmission dynamics of *Schistosoma japonicum* in the lakes and marshlands of China. *PLoS one*. 2008;3(12):e4058.

- 38) Gomes Casavechia MT, de Melo GAN, Da Silva Fernandes ACB, et al. Systematic review and meta-analysis on *Schistosoma mansoni* infection prevalence, and associated risk factors in Brazil. *Parasitology*. 2018;145(8):1000-1014
- 39) Bamgbola OF. Urinary schistosomiasis. *PediatrNephrol*. 2014;29(11):2113-2120
- 40) Tiongco RE, Paragas NA, Dominguez MJ, Lasta SL, Pandac JK, Pineda-Cortel MR. ABO blood group antigens may be associated with increased susceptibility to schistosomiasis: a systematic review and meta-analysis. *J Helminthol*. 2018; 94:e21.
- 41) Hassan AS, Zelt NH, Perera DJ, Ndao M, Ward BJ. Vaccination against the digestive enzyme Cathepsin B using a YS1646 *Salmonella enterica Typhimurium* vector provides almost complete protection against *Schistosoma mansoni* challenge in a mouse model. *PLoS Negl Trop Dis*. 2019;13(12):e0007490
- 42) Nelwan ML. Schistosomiasis: Life Cycle, Diagnosis, and Control. *Curr Ther Res Clin Exp*. 2019;91:5-9
- 43) WHO: *Salmonella*. 2010,[<http://www.who.int/mediacentre/factsheets/fs139/en/>]
- 44) Bamgbola OF. Urinary schistosomiasis. *PediatrNephrol*. 2014;29(11):2113-2120
- 45) Costain AH, MacDonald AS, Smits HH. Schistosome Egg Migration: Mechanisms, Pathogenesis and Host Immune Responses [published correction appears in Front Immunol. 2019 Apr 11;10:749]. *Front Immunol*. 2018;9:3042.
- 46) Osakunor DNM, Munk P, Mduluzi T, et al. The gut microbiome but not the resistome is associated with urogenital schistosomiasis in preschool-aged children. *Commun Biol*. 2020;3(1):155
- 47) King CH, Sutherland LJ, Bertsch D. Systematic Review and Meta-analysis of the Impact of Chemical-Based Mollusciciding for Control of *Schistosoma mansoni* and *S. haematobium* Transmission *PLoS Negl Trop Dis*. 2015;9(12):e0004290
- 48) Zwang J, Oliaro P. Efficacy and safety of praziquantel 40 mg/kg in preschool-aged and school-aged children: a meta-analysis. *Parasit Vectors*. 2017;10(1):47
- 49) Chen G, Dai Y, Chen J, et al. Oral delivery of the Sj23LHD-GST antigen by *Salmonella typhimurium* type III secretion system protects against *Schistosoma japonicum* infection in mice. *PLoS Negl Trop Dis*. 2011; 5(9):e1313.
- 50) Ashour DS, Othman AA. Parasite-bacteria interrelationship [published online ahead of print, 2020 Aug 4]. *Parasitol Res*. 2020;10.1007/s00436-020-06804-2

- 51) Abruzzi A, Fried B. Coinfection of *Schistosoma* (Trematoda) with bacteria, protozoa and helminths *AdvParasitol.* 2011;77:1-85
- 52) Degarege A, Degarege D, Veledar E, et al. *Plasmodium falciparum* Infection Status among Children with Schistosoma in Sub-Saharan Africa: A Systematic Review and Meta-analysis. *PLoS Negl Trop Dis.* 2016;10(12):e0005193
- 53) Chacha F, Mshana SE, Mirambo MM, et al. Salmonella Typhi meningitis in a 9-year old boy with urinary schistosomiasis: a case report. *BMC Res Notes.* 2015;8:64
- 54) Yunshan He et al (2019). Influence of *Debaryomyces hasnesenii* on bacterial lactase gene diversity in intestinal mucosa of mice with antibiotic-associated diarrhoea. *PLOS ONE* 14(12):e0225802
- 55) Modebe AA, Nnachi AA, Ukaegbu AA, Tata N, Agha MV, Udu-Ibiam OE, Nnachi IA “Dual infections of Enteric *Salmonella* species with *Schistosoma mansoni* among Patients from Two Hospitals in Jos, Nigeria.” *Journal of Applied & Environmental Microbiology*, vol. 2, no. 4 (2014): 198-202.
- 56) Lehman, J. S., Jr. ; Higashi, G. I. ; Bassily, S. ; Farid, Z. (1975). Rheumatoid factors in *Salmonella* and *Schistosoma* infections *Transactions of the Royal Society of Tropical Medicine and Hygiene* (66) 1 pp.125-9
- 57) Zhu X, Chen L, Wu J, Tang H, Wang Y. *Salmonella typhimurium* Infection Reduces *Schistosoma japonicum* Worm Burden in Mice *Sci Rep.* 2017;7(1):1349. Published 2017 May 2. doi:10.1038/s41598-017-00992-1
- 58) LoVerde PT, Amento C, Higashi GI. Parasite-parasite interaction of *Salmonella typhimurium* and *Schistosoma*. *J Infect Dis.* 1980;141(2):177-
- 59) Njunda A, Oyerinde J: *Salmonella typhi* infection in *Schistosoma mansoni* infected mice. *West Afr J Med.* 1996, 15: 24-30.
- 60) Mekonnen, A., Legesse, M., Belay, M. et al. Efficacy of Praziquantel against *Schistosoma haematobium* in Dulshatalo village, western Ethiopia. *BMC Res Notes* 6, 392 (2013)
- 61) Gal-Mor O, Boyle EC, Grassl GA. Same species, different diseases: how and why typhoidal and non-typhoidal *Salmonella enterica* serovars differ. *Front Microbiol.* 2014;5:391.
- 62) Gendrel D, Richard-Lenoble D, Kombila M, Engohan E, Nardou M, Moussavou A, Galliot A, Toure R: *Schistosoma intercalatum* and relapses of *Salmonella* infection in children. *Am J Trop Med Hyg.* 1984, 33: 1166-1169.

- 63) Crump J, Mintz E: Global trends in typhoid and paratyphoid Fever. *Clin Infect Dis*. 2010, 50: 241-246. 10.1086/649541.
- 64) Agoston K, Kerékgyártó J, Hajkó J, Batta G, Lefebvre D, Kamerling J, Vliegenthart J: Synthesis of fragments of the glycocalyx glycan of the parasite *Schistosoma mansoni*. *Chemistry*. 2002, 4: 151-161.
- 65) Antunes LC, Finlay BB. A comparative analysis of the effect of antibiotic treatment and enteric infection on intestinal homeostasis. *Gut Microbes*. 2011;2(2):105-108
- 66) Schneeberger PHH, Coulibaly JT, Panic G, et al. Investigations on the interplays between *Schistosoma mansoni*, praziquantel and the gut microbiome. *Parasit Vectors*. 2018; 11(1):168.
- 67) Foligné B, Plé C, Titécat M, et al. Contribution of the Gut Microbiota in P28GST-Mediated Anti-Inflammatory Effects: Experimental and Clinical Insights. *Cells*. 2019;8(6):577
- 68) Liu R, Cheng WJ, Tang HB, Zhong QP, Ming ZP, Dong HF. Comparative Metabonomic Investigations of *Schistosoma japonicum* From SCID Mice and BALB/c Mice: Clues to Developmental Abnormality of Schistosome in the Immunodeficient Host. *Front Microbiol*. 2019;10:440.
- 69) Kaiser P, Hardt WD. *Salmonella typhimurium* diarrhea: switching the mucosal epithelium from homeostasis to defense. *Curr Opin Immunol*. 2011;23(4):456-463
- 70) Ducarmon QR, Zwittink RD, Hornung BVH, van Schaik W, Young VB, Kuijper EJ. Gut Microbiota and Colonization Resistance against Bacterial Enteric Infection. *Microbiol Mol Biol Rev*. 2019; 83(3):e00007-19.
- 71) Cortés A, Peachey L, Scotti R, Jenkins TP, Cantacessi C. Helminth-microbiota cross-talk - A journey through the vertebrate digestive system. *Mol Biochem Parasitol*. 2019; 233:111222.
- 72) Zhao Y, Yang S, Li B, Li W, Wang J, Chen Z, Yang J, Tan H and Li J (2019) Alterations of the Mice Gut Microbiome via *Schistosoma japonicum* Ova-Induced Granuloma. *Front. Microbiol*. 10:352.
- 73) The PLOS Neglected Tropical Diseases Staff (2015) Correction: Differences in the Faecal Microbiome in *Schistosoma haematobium* Infected Children vs. Uninfected Children. *PLOS Neglected Tropical Diseases* 9(7): e0003969.
- 74) Nicholson, J. K., Connelly, J., Lindon, J. C. & Holmes, E. Metabonomics: a platform for studying drug toxicity and gene function. *Nat. Rev. Drug Discov*. 1, 153–161 (2002).

- 75) Hillier, S. D. et al. *Plasmodium falciparum* and helminth co-infection in a semi urban population of pregnant women in Uganda. *J. Infect. Dis.* 198, 920–927 (2008).
- 76) McGeachy MJ, McSorley SJ. Microbial-induced Th17: superhero or supervillain?. *J Immunol.* 2012;189(7):3285-3291
- 77) Sokol H, Pigneur B, Watterlot L, et al. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A.* 2008; 105(43):16731-16736.
- 78) Gryseels, B., Polman, K., Clerinx, J. & Kestens, L. Human schistosomiasis. *Lancet* 368, 1106–1118 (2006).