De-Worming in Developing Countries as a Feasible and Affordable Means to Fight Co-Endemic Infectious Diseases

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Abstract: Approximately one-third of humanity, especially in developing countries, is infected with parasitic roundworms or flatworms, collectively known as helminth parasites. These infections cause severe diseases, delayed physical development and mortality. A person in helminth endemic areas may be infected with these parasites all his life. These parasitic infections coincide with many other infectious diseases, such as malaria, tuberculosis and HIV. Treatment of these parasitic infections is relatively easy. In some cases a single dose of anti-parasitic treatment suffices. This paper briefly reviews the effects that helminthic infections have on other infectious diseases; on chronic non-transmittable diseases and discusses the potential benefits that de-worming may have on the overall morbidity and mortality associated with these diseases in developing countries, as well as on the effect de-worming may have on vaccination efficacy. We conclude that successful mass de-worming is essential for the reduction of the morbidity associated with these infections and may be a feasible and affordable means to combat other infectious diseases, such as HIV, malaria and tuberculosis. Furthermore, without it, HIV, malaria and TB vaccines may fail to confer protection in helminth endemic areas.

Keywords: Helminths, de-worming, developing countries, infectious diseases.

INTRODUCTION

Helminths are multicellular eukaryotic parasites that infect approximately one-third of the world's population and are one of the most common infections in poor people living in the developing world [1-3]. Some helminthic infections also occur in the developed world [4-6]. Helminths belong to two major groups of animals, the flatworms or Platyhelminthes (flukes and tapeworms) and the roundworms or Nematoda. The most serious helminth infections are acquired in poor tropical and subtropical areas [1], and constitute 85% of a class of diseases commonly referred to as Neglected Tropical Diseases (NTD) [2,7].

Many potential helminthic infections are eliminated by host defenses; others become established and may persist for prolonged periods, even years. In many cases the same individual may be infected by more than one parasite [8,9]. Although helminthic infections are often asymptomatic, severe pathology can occur [1]. The most obvious forms of direct damage are those resulting from the blockage of internal organs or from the effects of pressure exerted by growing parasites. In addition, many helminths undergo extensive migrations through body tissues, which both damage tissues directly and initiate hypersensitivity reactions. Immune-mediated inflammatory changes occur in the skin, lungs, liver, intestine, CNS, and eyes as worms migrate through these organs. Some helminthic infections are among the major causes of anemia in developing countries, with hookworm accounting for up to 73% of the severe iron-deficiency anemia in Africa [10,11]. Infection by helminths results also in chronic immune activation leading to immune dysregulation and immunological unresponsiveness of the host [12,13]. We [14-21] and others [22] have postulated that these profound immune changes significantly compromise the host capacity to cope with other infections, increase its susceptibility to infections and undermines the capacity of the host to mount effective immune responses to immunogens and vaccines (see below).

In many parts of the developing world, but especially in sub-Saharan Africa, the geographic overlap between helminthic infections, HIV/AIDS, tuberculosis (TB), and malaria is extensive [8,13,18,23] (Fig. **1**). For example, there are several reports showing rates of 25% and higher of helminth and HIV-1 co-infections [24-32]. Helminth infections also occur in HIV-1 infected tuberculosis patients (e.g. [33]). Helminth infections may also overlap with chronic diseases such as obesity, cardiovascular disease, allergy, and diabetes.

Treatments of helminthic infections are relatively simple. Effective treatment and prevention strategies can be delivered for less than US$1 per capita per year [8]. De-worming programs, throughout the world, have shown significant improvement in childhood growth, physical fitness, cognition, and hemoglobin and serum ferritin concentrations [8]. This year alone, hundreds of millions of the world's poorest people will receive a single annual dose of one or more drugs to treat their parasitic worm infections [34].

This paper briefly reviews the effects that helminthic infections have on other infectious diseases and chronic non-transmittable diseases, and discusses the potential benefits and feasibility that treatment of helminthic infections may have on the overall morbidity and mortality associated with several of the most prevalent infections and diseases in developing countries, especially on HIV-1 progression. Finally, this paper discusses the plausible effects that hel-

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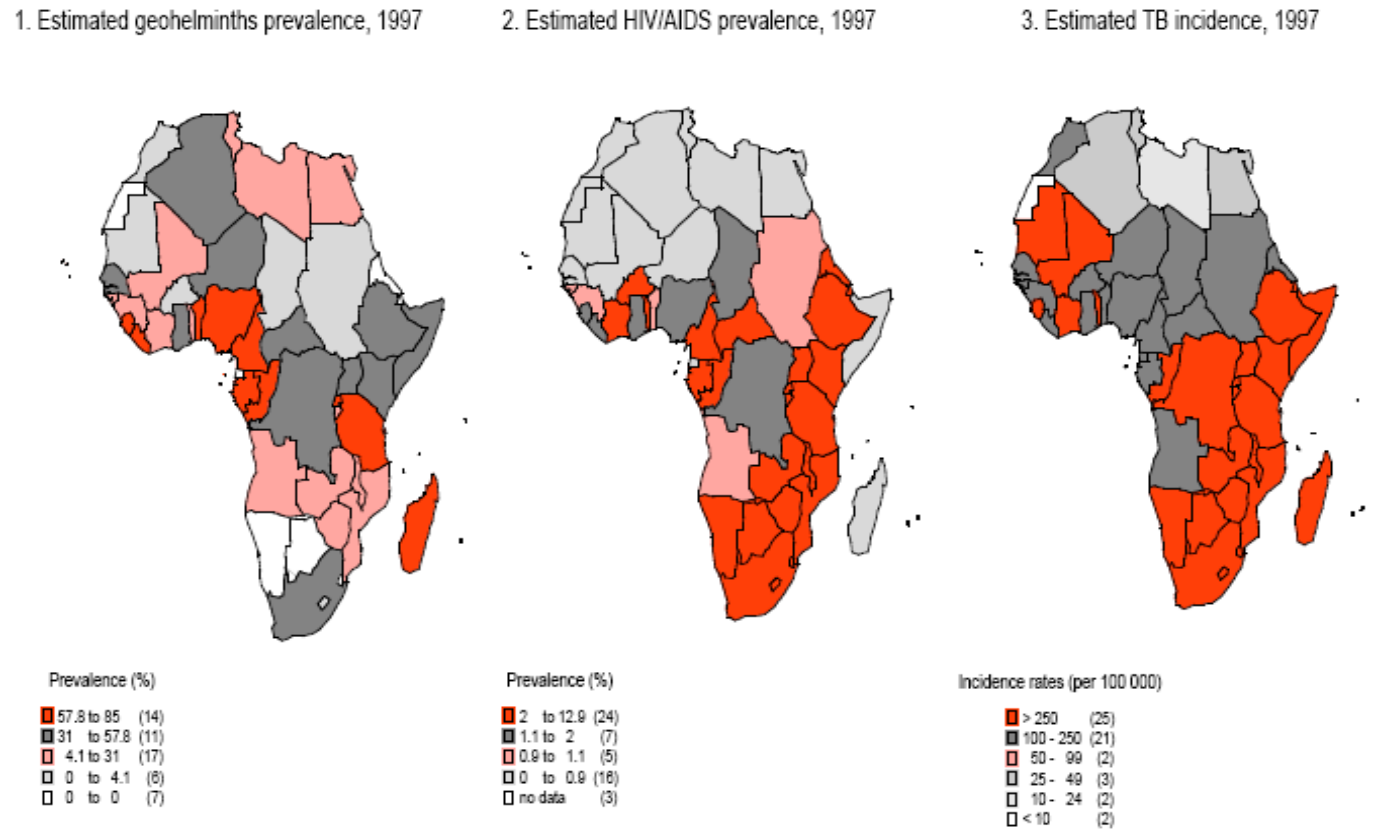

Fig. (1). Similar geographic distribution of geohelminths, HIV and MTB in Africa (Data from Ref. [116]).

minthic infections may have on the efficacy of vaccination aimed at the prevention of other infectious diseases.

HELMINTHIC INFECTIONS RESULT IN CHRONIC IMMUNE ACTIVATION AND DYSREGULATION, AND A DOMINANT TH2 CYTOKINE PROFILE.

Helminthic infections bring about several changes in the immune profile of the host that have a major impact on the host ability to respond immunologically and they consist of the following (reviewed in [13,35]): i) an imbalance in the peripheral lymphocyte populations; ii) a dominant Th2 immune profile; iii) increased levels of immune suppressive cytokines and negative T cell activation regulators; iv) impairment of cellular immune responses, with decreased delayed type skin hypersensitivity and impaired cell proliferation to recall antigen; v) T-cell signal transduction impairments and anergy; vi) increase in T regulatory/suppressor cells (CD25+CD4+ cells); vii) increased expression of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which is a negative modulator of immune effector mechanisms and cell proliferation [36]; viii) impaired Toll-like receptor 9 (TLR9) expression [37]; x) Increased proportion of cells expressing the chemokine receptors CCR5 and CXCR4 with lower levels of chemokine secretion (RANTES and MIP-1α), by CD8+ cells; and xi) diminished responsiveness to CpG-DNA stimulation [20,37].

The ability of the host to mount an immune response and the nature of that response, are greatly determined by the preexisting state of the immune system. Thus, the TH2 skewed immune profile associated with the helminthic infections, influences the host's immune response towards a TH2 type of response, as observed by several investigators [38-46]: i) in the presence of a dominant TH2 profile, the immune response to other antigens, is skewed towards a TH2 type of response; ii) the ability to mount a cellular response, such as the generation of HIV specific cytotoxic T lymphocytes (CTL), is impaired in *Schistosoma* infected (TH2 dominant) animals; iii) suppressed immune response and anergy will accompany chronic helminthic infection; and iv) the specific immune response to geohelminths diminishes with progression of the infection and with helminth load. Taken together, all these findings clearly indicate that the immune system of the helminth-infested host is profoundly changed and therefore is expected to behave quite differently from that of the uninfected host.

Several studies support the notion that not the TH1 to TH2 shift, but rather other cytokines, primarily TGF-β, mediate the antigen-specific hyporesponsiveness characteristic to chronic human or primate helminth infections (Reviewed in [13]). One possible way through which TGF-β down regulates T cell responses is via upregulation of Cbl-b, an intracellular upstream negative regulator of T cell activation [47-49]. Cbl-b sets the threshold of signaling in T and B cells [49]. We have found that stimulation of peripheral blood mononuclear cells (PBMC) with TGF-β increases the intracellular pools of Cbl-b [50]. This, together with the increased levels of expression in T cells of the downregulator CTLA-4 that is found in helminth infected individuals [12,50], raises the threshold for effective T cell activation [51], and may explain the reduced proliferation, following anti-CD3 stimulation, and reduced phosphorylation of

ERK-1/2, following phorbol myristate acetate (PMA) and Ca^{++}-ionophore stimulation, of PBMC obtained from helminth infected immune activated individuals [12,18].

Importantly, most of the above described immunological impairments, which clearly compromise the capacity of the helminth infected individuals to mount effective immune responses to pathogens as well as to vaccinations, are reverted almost completely, following eradication of the helminthic infections [13,20,52-55].

HELMINTHS AND HIV-1

The role of the TH1/TH2 types in the pathogenesis of HIV has been studied extensively [56,57]. Though there is no general agreement as to the role of these responses in every phase of the infection, there are some important findings that clearly bear on the response type in different stages: i) activated CTL are responsible for the initial clearance of the primary viremia and probably for maintaining low viremia during the asymptomatic phase of the infection [58-60]; ii) progression of the infection is accompanied by a TH1 to TH2 switch, with a reduction in the number of TH1 clones and an increase in the number of T-helper type 0 (TH0)/TH2 clones [61-63]; iii) TH1 functions are correlated with better survival and slower progression [57,64]; iv) TH0 cells (non-differentiated cells) or TH2 cloned cells show increased susceptibility for HIV infection and replication [62]; and v) progression may be correlated to reduction of cellular immunity, together with higher permissiveness of TH0/TH2 cells to HIV infection [62]. Hence, protection from HIV infection may also be associated with an effective TH1 cellular defense. The best evidence is found in individuals that have been exposed to HIV and yet remained HIV seronegative while having specific HIV cellular immunity [64-70], and HIV seronegative infants born to HIV infected mothers and having HIV specific CTL activity [71]. The importance of cellular immunity in conferring protection from infection has also been shown in several studies of protective vaccination to SIV in primates [72-74]. Helminth co-infection is associated with increased risk of mother to child transmission of HIV, possibly by a mechanism in which parasite antigens activates lymphocytes in utero [25]. In primates it has been demonstrated that *Schistosoma* infected monkeys required significantly less simian-human immunodeficiency virus (SHIV) to get infected with the virus in comparison to schistosome non-infected animals [75].

We have previously suggested that the chronic immune activation and the TH2 immune profile caused by helminthic infections are major factors in the pathogenesis of AIDS in Africa, which may account for the different behavior of the epidemic in Africa- its rapid spread and probably its faster progression [14]. Though the issue of faster progression of HIV infection in Africa is controversial, and there is a paucity of controlled studies on the natural course of HIV in Africa [14], there are also studies from other developing countries in Asia and the Caribbean, which clearly demonstrate faster progression of HIV infection in these countries [76-79]. Overall, our hypothesis is supported by the following observations: i) similar immune activation and dysregulation of peripheral T cell populations has been observed in other parts of Africa and in India, where helminthic infections are endemic [80,81]; ii) the similar distribution and mutual enhancement of HIV occurs mostly in the poor populations where helminthic infections are extremely common [82,83]; iii) the chronic immune activation due to helminthic infections is associated with increased expression of HIV co-receptors, both CCR5 and CXCR4, as well as with increased susceptibility for HIV infection *in vitro* [84-87]; iv) plasma HIV viral load is higher in people living in Sub-Saharan Africa, where helminth infections are extremely prevalent [88]; v) faster progression to AIDS has been documented in Africa and Asia in areas endemic for helminths [88-91] and becomes similar to western rate, once helminthic infections are eradicated [92]; and vi) helminthic load (number of eggs excreted in the stool) is correlated with increased HIV plasma viral load [18].

Based on the above, it is clear that helminthic infections may adversely affect HIV-1 susceptibility and disease progression, thus requiring a means of eradicating the helminthic parasites that may affect HIV pathogenesis. Multiple observational studies suggest possible benefit in reducing plasma viral load and increasing CD4 counts in HIV-1 helminth coinfected individuals following anti-helminthic treatment (Reviewed in [13,20,21,93]. These observational studies were strongly supported by three randomized controlled trials that evaluated the effects of de-worming on markers of HIV-1 disease progression in helminth and HIV-1 co-infected individuals (Reviewed in [94]). All 3 trials demonstrated benefit in attenuating or reducing plasma viral load and/or increasing CD4 counts. For example, treatment of *Ascaris lumbricoides* with albendazole in HIV-1-coinfected adults resulted in an increase of 109 CD4+ cells per μl ($p = 0.003$) and a trend for 0.54 log10 lower HIV-1 RNA levels ($P = 0.09$) during 3-month follow-up [95]. Given the high prevalence of *A. lumbricoides* infection worldwide (807 million infected individuals) and a 4.2 billion population at risk [1], de-worming may be an important potential strategy to delay HIV-1 progression [95].

HELMINTHS AND OTHER INFECTIOUS DISEASES

Plasmodium infections, which lead to malaria, are considered the most deadly infections in tropical areas [96]. Several studies (reviewed in [97]) show enhanced risk or increased incidence of clinical malaria resulting from either soil-transmitted helminths or schistosome infections. It has been hypothesized that the increased malaria susceptibility results from a shift in the host humoral responses from malaria-protective, cytophilic humoral antibodies to non-protective, non-cytophilic subclasses [97]. One of the major clinical manifestations of malaria is anemia. In the case of hookworm and malaria, it has been shown that anemia from hookworm and anemia from malaria can build on each other to produce profound reductions in hemoglobin [8]. This severe anemia resulting from helminth polyparasitism and malaria produces several adverse health consequences among pregnant women, children, and individuals with HIV [8]. In pregnancy, anemia is a leading contributor to maternal morbidity and mortality; it is associated with shock; risk of cardiac failure; decreased ability to work, and adverse perinatal outcomes. In young children, anemia is associated with increased child mortality, and impairments in physical

growth, cognitive and motor development, and immune function. Among individuals with HIV, anemia is an independent risk factor for early death. The effect of helminthic infections on *Plasmodium*-specific immune responses is controversial and deserves further studies.

Tuberculosis is the second major co-infection whose prognosis is associated with parasitemia. Like malaria, the impact of intestinal helminth infection on *Mycobacterium tuberculosis* (MTB)-specific immune responses during active tuberculosis was carefully studied. In a recent study it has been found that concomitant intestinal helminth infection in patients with newly diagnosed TB skews their cytokine profile toward a TH2 response [98], which favors persistent MTB infection and a more protracted clinical course of the disease. Additionally, in a cohort of HIV-infected Ugandan adults, a type 2 cytokine bias and eosinophilia were associated with progression to active TB [99]. There is some evidence that helminth infections, especially hookworm and schistosomiasis, adversely affect the outcome of pulmonary tuberculosis or the progression to active tuberculosis [18,100], and reduce the T cell responses in individuals receiving Bacillus Calmette–Guerin (BCG) [101-103]. Ellias et al. have shown that chronic worm infection reduces the immunogenicity of BCG in humans and this was associated with increased TGF-beta production but not with enhanced Th2 immune response [104]. However, the data supporting this concept is still not conclusive.

HELMINTHS AND CHRONIC NON-INFECTIOUS DISEASES

Chronic non-infectious diseases include cardiovascular conditions (mainly heart disease and stroke), some cancers, chronic respiratory conditions, and type 2 diabetes [105]. Together they account for 60% of all deaths worldwide with approximately 80% of them occurring in low-income and middle-income countries [105]. With this in mind, oxidative stress has been implicated as an important pathogenic factor in the pathophysiology of various life-threatening diseases such as cancer, cardiovascular diseases and diabetes. [106]. Oxidative stress occurs when the production of free radicals overcome the antioxidant defense in the body. Interestingly, hydrogen peroxide (H_2O_2), lipid peroxidation and advanced oxidative protein product (AOPP), all markers of oxidative stress, were significantly higher in the urine of human subjects whose stools were infected with parasites such as *Blastocystis hominis*, *Ascaris, Trichuris*, hookworm and microsporidia, than in non-infected individuals [107]. This suggests that the elevated oxidative stress in humans infected by intestinal parasites may exasperate the development of chronic non-infectious diseases in the parasite infected individuals.

The etiological role of parasitic infection has been well established, through epidemiological studies, for many chronic diseases prevalent in the tropics [108]. Examples of this include *Schistosoma mansoni* infection leading to portal hypertension; *Schistosoma haematobium* infection leading to obstructive uropathy and squamous cell carcinoma of the bladder; *Clonorchis sinensis* leading to cholangiocarcinoma; and *Taenia solium* infection leading to epilepsy. The pathogenesis of these relations is still undefined but offers tenuous associations such as schizophrenia with toxoplasmosis and link malignancy and epilepsy with a range of helminthic infections. *S. mansoni* infection is of particular importance because it is linked to insulin uptake and potentially diabetes. Schistosomes have two insulin receptors (SmIR-1 and SmIR-2), which allow insulin to regulate glucose uptake [109]. This regulation may have an impact on host blood glucose levels and insulin production. Persistent *S. mansoni* infection is also linked to a chronic Th2 response which induces severe pathological changes in the gut and liver [110].

DE-WORMING AND VACCINE EFFICACY

Protective HIV-1 vaccines are clearly the only realistic solution to stop the AIDS epidemic. It is quite accepted by the scientific community that a protective HIV vaccine should not only generate neutralizing antibodies but also potent long-lived TH1 dependant memory $CD8^+$ CTL [74]. We have hypothesized that in developing countries chronic parasitic infection adds another level of complexity to AIDS vaccine development by causing a constant state of immune activation characterized by a dominant Th2 type of cytokine profile, high IgE levels, and eosinophilia [17,93,111].

It may be that the dominant pre-existing TH2 profile undermines the ability to generate a TH1 type of response and therefore HIV specific cellular immunity [112]. This has been clearly shown previously in the study of the murine model of Schistosomiasis, where infected animals with a preexistent TH2 immune profile were not able to mount CTL responses against HIV envelope peptides, while the normal non-infected animals could do so [42]. Thus, eradication of the helminthic infections may be a prerequisite for effective HIV-1 immunization, as we have suggested [17,20,21], or that an HIV-1 vaccine should be designed so as to induce Th1 dependent immune responses in spite of the preexistent TH2 immune background. We demonstrated the capacity to generate specific potent TH1 immune responses, including to an HIV-1 antigen, in *Schistosoma*-infected mice with preexistent TH2 profile, by the use of potent TH1 inducing adjuvants [113,114].

Immunomodulation and TH2-biased pre-existing immune profile caused by helminthic infections may also have an impact on the host response to mycobacterial vaccination [17,18,22,103,104]. The only vaccine available against tuberculosis, BCG, so effective in experimental animal models, has shown poor results especially in areas of high TB incidence with a high prevalence of intestinal helminth infections [22]. In a study in which the efficacy BCG vaccination was determined after anti-helminthic therapy, mycobacterial antigen-specific cytokine responses were significantly higher in PBMC obtained from the de-wormed studied group. The increased immunogenicity of BCG was associated with increased TGF-beta production but not with enhanced Th2 immune response. We also have found decreased capacity of PBMC obtained from helminth infected individuals to proliferate following stimulation with Tuberculin purified protein derivative (PPD), a TB specific antigen [18]. A sequential follow-up revealed significantly higher proliferation of PBMC to PPD in 7 out of 8 examined individuals six months after de-worming [18]. In accordance

with the above, it has been shown that *S. mansoni* infection reduces the protective efficacy of BCG vaccination against virulent *M. tuberculosis* in infected mice [103].

In a similar study as above, while mice immunized with a malaria vaccine were protected following malaria challenge, mice co-infected with a nematode (*Heligmosomoides polygyrus*) failed to mount a protective immune response [115]. The immunized nematode-infected mice produced significantly lower levels of malaria-specific antibody than the nematode-free mice. Furthermore, de-worming treatment of *H. polygyrus*-infected mice before anti-malarial immunization, but not de-worming treatment after anti-malarial immunization, restored the protective immunity to malaria challenge [115].

CONCLUSION

Helminth infections are endemic in most of the developing countries, where other infectious diseases, such as AIDS, malaria and tuberculosis, are also highly predominant. Removing these parasites is, in itself, important so as to reduce the mortality and morbidity associated with these infections. Furthermore, we suggest that removal of these parasites may be important in the context of fighting other infectious and non-infectious diseases. This is based on the clear understanding and supporting data showing that helminthic infections have profound debilitating effects particularly on the immune system of the host, potently compromising the host capacity to cope with other infections and to mount efficacious immune responses. In addition, it may be that without the eradication of helminthic parasites, HIV, malaria and TB vaccines would fail to confer protection in helminth endemic areas, implying that eradication of helminthic infections, or modulation of the immune change that they cause, should be instituted prior to HIV, malaria and TB mass vaccination. Since the public health case for de-worming has already been demonstrated by its effectiveness in enhancing the development of children, large-scale eradication of helminthic infections throughout the poor world in the context of the AIDS and tuberculosis epidemics is feasible and should be seriously considered and implemented, even if the consequences are only probable or partially positive.

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