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Preventive Treatments of Tropical Infections and Associated Anaemia in Children: Review of Effectiveness and Implications for Strengthening Child and Community Health Services in Developing Countries

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Abstract

Objectives: We reviewed studies conducted on patho-physiology, burden and effectiveness of preventive treatments of tropical infections and associated anaemia in children in developing countries. Interventions required to strengthen child and community health services aimed at complimenting preventive treatments and alleviating the burden of the diseases were suggested.

Methods: Literature from Pubmed (MEDLINE), AJOL, Google Scholar and Cochrane database were reviewed.

Results: Evidence abounds on the effectiveness of preventive treatments of tropical infections and associated anaemia in children living in developing countries. Yet, the infections remain an important cause of morbidity and mortality in the age group. Effectiveness of preventive treatments can be complemented by individual, household and community actions aimed at interrupting disease transmission.

Conclusion: Gains of preventive treatments of tropical infections and associated anaemia in children can be consolidated by strengthening child and community health services in developing countries.

Keywords: Tropical infections; Anaemia; Preventive treatment; Community health; Children

Introduction

Anaemia is a global health problem in both developing and developed countries with major consequences on human health [1]. Anaemia is the world's second leading cause of disability [2]. The World Health Organization (WHO) estimated the number of anaemic persons to be about 2 billion worldwide and approximately 50% of all cases can be attributed to iron deficiency [3]. Anaemia is responsible for about 1 million deaths a year, out of which three-quarters occur in Africa and South-East Asia [4].

About half of all school children in developing countries including Africa and Asia suffer from anaemia [5]. Chronic anaemia during childhood is associated with impairments in physical growth, cognition, and school performance [6]; furthermore, severe anemia accounts for up to half of the malaria-attributable deaths in children younger than 5 years of age [7]. In Africa for example, severe anaemia probably accounts for more than half of all childhood deaths [8].

Pre-school age children account for 10%–20% of the 2 billion people worldwide who are infected with Soil-Transmitted Helminths (STHs) [9]. Millions of people in sub-Saharan Africa are infected with Neglected Tropical Diseases (NTDs) such as schistosomiasis (200 million), hookworms (198 million), *Ascaris lumbricoides* (173 million) and *Trichuris trichiura* (182 million) among others [10-12]. About 45.1 million (25%) school-aged children in sub-Saharan Africa are at coincidental risk of hookworm and malaria infections [13]. Therefore, the most intense infections with the commonest worms occur in school-age children who have low protective immunity against malaria [14]. All of these can result in anaemia and further worsen the disease cases in these children.

Methods

We reviewed relevant studies conducted on patho-physiology, burden and effectiveness of preventive treatments of tropical infections and associated anaemia in children in developing countries. The following search terms were used: patho-physiology, burden, tropical infections, malaria, soil-transmitted infections, schistosomiasis, anaemia, preventive treatments and developing countries. Cross sectional, observational and randomized control trials' literature on the subject published between 2000 and 2011 served as the main sources of information. These literature were obtained from the commonly used medical databases such as PubMed (Medline), AJOL and Google Scholar; in addition, Cochrane Library was used as a source for systematic reviews on the subject matter.

Results

Patho-physiology

Malaria reduces heamoglobin concentrations through a number of mechanisms; principally by destruction and removal of parasitized red cells, shortening of the life span of non-parasitized red cells, and decreasing the rate of erythrocyte production in the bone marrow [15]. Some of the mechanisms that cause anemia during a malaria illness such as heamolysis and cytokine disturbances are associated more with the acute clinical states, whereas chronic or repeated infections are more likely to involve dyserythropoiesis [16].

Hookworm causes iron deficiency anemia through the process of intestinal blood loss [12]. Adult hookworms burrow deep into the

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mucosa and sub-mucosa of the small intestine, eventually rupturing capillaries and arterioles [12,17]. Infection with 25–30 adult *Necator americanus* hookworms results in at least 1 ml of blood loss per day-a volume containing an amount of iron roughly equivalent to the daily requirement of an adolescent boy or girl and slightly more than the daily requirement of a younger child [18,19].

Schistosomiasis causes anaemia by chronic blood loss as eggs penetrate the wall of the bowel (in intestinal schistosomiasis) and the urinary tract (in urinary schistosomiasis), thereby invading the walls and causing bleeding [20]. The anaemia associated with schistosomiasis has been attributed to several mechanisms, including iron deficiency due to blood loss in the stool or urine, splenic sequestration leading to destruction of erythrocytes, autoimmune haemolysis, and the chronic inflammatory response to schistosome eggs deposited in host tissues [20,21].

Burden of tropical infection-induced anaemia

Preliminary analyses of spatial congruence suggest that as many as one quarter of African school children may be coincidentally at risk of *Plasmodium falciparum* and hookworm infections, [13] which may then predispose them to anaemia. In African areas of stable endemic malaria transmission, between 17.9 and 32.1 million children 5–14 years of age are estimated to be at risk of co-infection with *P. falciparum* and different helminthes, with the risk greatest for hookworm [22] and thus enhancing the risk of anaemia.

An estimated 4.5 billion individuals are at risk of Soil-Transmitted Helminthic (STH) infections and more than one billion individuals are thought to be infected. Out of these, 450 million suffer morbidity from the infections, the majority of whom are children [23]. Severe worm infections due to helminthes in children can lead to iron deficiency anaemia, protein energy malnutrition, stunting and wasting. Hookworm infestation is a leading cause of iron-deficiency anemia that afflicts an estimated 576 million people throughout developing nations of the tropics, with highest prevalence in East Asia/Pacific Islands and sub-Saharan Africa [24]. Anaemia and its co-morbidities like heavy worm infestation have also been shown to affect cognitive function in children [25].

In sub-Saharan Africa, 112 million people are infected with *Schistosoma haematobium*, with the most intense infections occurring in children 5–15 years old [26]. Children have the highest prevalence and intensity of soil-transmitted helminthic and schistosomal infections; however, the consequences of chronic infection such as anaemia, growth stunting, hepatic/urinary fibrosis, and impaired cognitive development continue to have an effect throughout adulthood [27]. Therefore, iron supplementation and de-worming have been shown to effectively improve cognitive performance and educational achievement [28,29].

A review of effectiveness of preventive treatments for tropical infections and associated anaemia in children

In view of the afore-mentioned burden, the World Health Organization (WHO) advocates cost-effective preventive chemotherapy, and encourages all its member states to integrate Neglected Tropical Diseases (NTDs) control intervention strategies in order to control co-morbidity due to co-infections [30]. Similarly, the World Bank listed regular de-worming of children as one of the most cost-effective health interventions a developing nation can undertake [31].

Furthermore, the World Health Assembly Resolution 54:9 encouraged member states to reach at least 75% of school-aged children with regular annual de-worming in moderate to high transmission zones by 2010 [32]. To this end, the World Health Assembly (WHA) passed resolution 54.19 endorsing regular treatment of high-risk groups, particularly school-aged children, as the best means of reducing morbidity and mortality [33]. The WHA therefore recommended that member states should sustain successful control activities in low-transmission areas in order to eliminate schistosomiasis and soil-transmitted helminthic infections as a public health problem. In areas of high transmission, WHA recommended that high priority be given to implementing or intensifying control of schistosomiasis and soil-transmitted helminthic infections while monitoring drug quality and efficacy is conducted. This is all aimed at attaining a minimum target of regular administration of chemotherapy to at least 75% and up to 100% of all school-aged children at risk of morbidity by 2010 [33].

Preventive treatments for Malaria: Chemoprophylaxis has been shown to be highly effective at reducing malaria-related mortality and morbidity. Studies done in West Africa (Senegal and Mail) have shown that seasonal Intermittent Preventive Treatment (IPT) could be an effective malaria prevention strategy among children younger than 5 years of age in areas of seasonal malaria transmission [34,35].

The most studied drug for intermittent preventive treatment is sulfadoxine-pyrimethamine [36]. A recent analysis of pooled efficacy data from six randomized trials of sulfadoxine-pyrimethamine given to infants (IPTi) showed that compared with placebo, the intervention had a protective efficacy of 30.3% against clinical malaria, 21.3% against anaemia (haemoglobin <80 g/L or packed-cell volume <25%), and 38.1% against hospital admissions associated with malaria parasitaemia, but no effect on mortality [37].

In Kenya, a cluster randomised intermittent preventive treatment trial with a full course of anti-malarials - Sulfadoxine-Pyrimethamine (SP) and Amodiaquine (AQ) - given once during a school term, irrespective of whether the children were infected or not was conducted. Findings showed a 48% reduction in the rates of anaemia and a large effect size of 0.48 Standard Deviations (SD) on children's sustained attention in class [38]. In another study undertaken in Niakhar, Senegal, an area of intense but short seasonal malaria transmission, SP and one dose of Artesunate (AS) given to children less than 5 years old three times at monthly intervals throughout the peak period of malaria transmission reduced clinical attacks of malaria by 86% [35].

In another comparative study carried out in Ghana among children aged 3-59 months, monthly Amodiaquine (AQ) plus AS was compared with bimonthly AQ plus AS and bimonthly SP. Monthly AS plus AQ was the most effective regimen, which gave protection against clinical episodes of malaria by 69% and anaemia by 45% compared to bimonthly SP which reduced the incidence of malaria by 24% and anaemia by 30% and bimonthly AQ plus AS which reduced the incidence of malaria by 17% and anaemia by 32% [39]. It is noteworthy, however, that despite the realization that preschool children in malaria-endemic countries are vulnerable to severe malaria and the potential benefit they could derive from prophylaxis, the WHO does not recommend this drug combination as prophylaxis for this age group. This is due to unresolved controversies on possible adverse consequences of prolonged prophylaxis and difficulties that could attend large-scale delivery of the intervention [40,41]. On the other hand, WHO has recommended IPT with sulfadoxine-pyrimethamine for infants in areas of Africa with moderate to high malaria transmission and low resistance to this drug combination [42].

In a randomized controlled trial study of IPTi done in Tanzania using a single dose of Sulfadoxine-Pyrimethamine (SP), findings showed that infants obtained a 50% protective efficacy against severe anaemia [43]. Similar results were obtained from a study done among infants aged 12-16 weeks conducted in northern Tanzania using amodiaquine as IPT with protective efficacy of preventing malaria by 64.7% as compared with using a placebo (iron supplements only) of preventing malaria by 59.8% [44]. A review of 21 randomized controlled trials done in Africa on both prophylaxis and intermittent treatment reported consistent reduction of clinical malaria and admission to hospital [45].

Preventive treatments for helminths (Hookworm, Ascariasis, etc): Periodic de-worming for soil transmitted helminthes has been shown to improve growth, micronutrient status (iron and vitamin A), and motor and language development in preschool age children. Thus, a strong case has been made for inclusion of this age group of children in control programmes which are carried out in areas where soil-transmitted helminthic infections are prevalent [9].

In 2006, the World Health Organization recommended a reduction in the threshold of helminthic infection through mass treatment in a simplified strategy called "preventive chemotherapy" [31]. Mass treatment is recommended for all school-age children once a year if 20% to <50% of children are infected with intestinal nematode worms while twice a year mass treatment is recommended if ≥ 50% of children are infected [31]. There is a preference by a school of thought that a periodic administration of anti-helminthics for controlling the infection may be better than aiming to achieve eradication because these programmes are focused on reducing intensity of infection and transmission potential, primarily to reduce morbidity and avoid mortality associated with the disease [9].

Findings from a study carried out in Zanzibar, Tanzania showed that anti-helminthic treatment significantly reduced the prevalence of anaemia and stunting among pre-school age children, who received mebendazole every 3 months for 1 year [46]. Another study conducted in Sierra Leone showed significant reductions of 65.2% and 87.9% in the prevalence and overall intensity of hookworm infection respectively six months following mass drug administration with mebendazole [33].

Likewise, a study done in Zimbabwe among school children showed that two rounds of de-worming and sustained prompt malaria treatment significantly reduced the proportions of children with helminthes -*Plasmodium falciparum* co-infections [47]. However, authors opined that this finding from combined treatment intervention might have been confounded by concomitant school based health education and consequent change in children's behaviour towards preventive practices [47]. WHO now recommends that anti-helminthic treatment should be provided to children from the age of 12 months in areas of high prevalence of helminthic infections [48,49].

Preventive treatments for Schistosomiasis: Praziquantel has been used extensively and successfully in national schistosomiasis control programmes in Brazil, China, Egypt, and the Philippines, and there is little evidence of the development of clinically relevant resistance [50]. Despite this, children aged 5 years and below are currently excluded from schistosomal control programmes for certain reasons. Firstly, there are operational difficulties associated with accessing preschool children; secondly, there are misconceptions about their level of exposure to infective water and thirdly, there is paucity of safety data on the drug of choice for schistosomal control i.e. praziquantel. Therefore, pre-school children may be at risk of infection and remain a potential reservoir for the parasite in communities which have been successfully targeted by mass anti-helminthic treatment [51]. Praziquantel is, however, administered as a drug of choice in control programmes to children above 5 years of age as they are assumed to be of school age.

A study done in Sierra Leone showed that mass drug administration of praziquantel resulted in significant reductions of 44.6% and 72.3% in prevalence and overall intensity of *Schistosomal mansoni* respectively [33]. Similar studies conducted in Niger and Burkina-Faso showed that a single praziquantel treatment significantly reduced both prevalence and intensity of *Schistosomal haematobium* infection in the large-scale national control programmes [52,53].

By targeting both hookworms and schistosomes, human helminthic vaccines are being developed to reduce parasite-induced morbidity. If administered in early childhood, it is thought that such vaccines could prevent major paediatric sequelae of these infections, including anaemia [54].

Conclusion and Recommendations

Tropical infections such as soil-transmitted helminthes and schistosomiasis, and their associated anaemia among children living in resource-limited endemic countries remain a huge burden to the health system and a matter of concern to health service providers. This is because of the short and long-term consequences of the infections, which not only may overwhelm the existing child health services but may also adversely affect the quality of life of the children.

Though, evidences abounds on the effectiveness of preventive treatments for these infections, however control strategies at individual, household and community levels are capable of eradicating or eliminating the diseases in endemic countries are paramount to alleviating the burden of the diseases. Therefore, such strategies should be given a high priority.

In the light of the above, capacity of health facilities and programmes providing child health services in endemic countries should be strengthened with laboratory support. The support should enable laboratories to conduct simple tests such as haematocrit estimation or packed cell volume, malaria parasite and stool and urine microscopy within the context of the setting. The laboratory capacity to conduct these tests would afford children, both pre-school and school, the opportunity to be routinely screened for anaemia, malaria, intestinal helminthiasis, and both urinary and intestinal schistosomiasis. These efforts would also provide evidence required for prompt and timely preventive treatments to be carried out.

At individual and household levels, improved personal and food hygiene practices such as adequate washing of hands, fruits and vegetables need to be emphasized as part of child health services; in addition, distribution and correct use of insecticide treated net for personal protection should be incorporated. This should be combined with carefully designed and packaged health education messages, which have taken into cognizance the routes of transmission of the infections and socio-cultural milieu of mothers and caregivers. Thus, health services and programmes for children such as child welfare services, child nutrition clinics and school health services should be strengthened with appropriate and adequate resources to provide these tasks routinely.

In addition, basic environmental measures which have been shown to be effective in interrupting transmission of the infections need to be intensified. Thus, interventions which would encourage clean environment and avoid human contact with excreta such as safe disposal of human excreta, prevention of soil contamination with faeces and discouraging promiscuous deposition of faeces round the houses and fields are a high priority to alleviating the burden caused by soil-transmitted tropical infections and therefore should be vigorously pursued [55]. This is particularly important as it is evident that current coverage of population by improved sanitation in countries of sub-Saharan Africa and Southern Asia averaged 30% and 41% respectively [56]. Specifically, between 11% and 27% of households and between 12% and 31% of the population in Ghana, Kenya and Nigeria have access to improved toilet facilities [57-59]. From the foregoing, it has been opined that most countries in the developing world are not on track to meet the Millennium Development Goal 7 (MDG7) Target 10 on sustainable access to basic sanitation [56].

The above assertion further underscores the importance of sanitation as a powerful indicator of the state of human development in any community because access to sanitation is known to bestow benefits at many levels. These studies have shown that the method of disposing human excreta is one of the strongest determinants of child survival and the transition from unimproved to improved sanitation reduces overall child mortality by about a third. Furthermore, improved sanitation results in advantages for public health, livelihoods and dignity and these extend beyond households to entire communities [60]. In view of the foregoing, it is imperative that local and national governments as well as international development partners renew their concerted efforts at providing sustainable access to basic sanitation for households and communities in resource-limited countries. It is suggested that the adopted human excreta methods should be culturally acceptable while household and community members are taught on the correct use of facilities.

In addition to improving basic sanitation, the school health programme in developing countries can consider provision of locally-made cheap shoes for school children as a strategy to preventing hookworm infection [55]. Environmental measures aimed at interrupting transmission of schistosomiasis and malaria in children should combine physical, chemical and biological activities. For example, children who work on farmlands, rice fields and similar environment with predisposition to water contacts should be provided with up-to-knee boots whereas a plank or log of wood can be used to improvise for a bridge across water bodies to avoid wading by children on their way to schools and market places. These efforts should be complimented by spraying an effective mollusce and/or introducing a predator of snail vectors into water bodies in the community. With respect to malaria, improved housing condition with door and window nets (whether insecticide-impregnated or not) as well as indoor and outdoor spraying of insecticides are effective strategies.

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