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Editorial

A new global strategy for the elimination of schistosomiasis

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ABSTRACT

Mass drug administration utilising a single oral dose of 40 mg/kg of praziquantel (PZQ) has been endorsed and advocated by the World Health Organisation (WHO) for the global control and elimination of schistosomiasis. However, this strategy is failing primarily because the drugs are not getting to the people who need them the most. The current global coverage is 20%, the drug compliance rate is less than 50%, and the drug efficacy is approximately 50%. Thus in reality, only about 5% of the reservoir human population is actually receiving intermittent chemotherapy. Despite claims that more of the drug will soon be made available the current strategy is inherently flawed and will not lead to disease elimination. We discuss the many practical issues related to this global strategy, and advocate for an integrated control strategy targeting the life cycle and the most at-risk. Moreover, we discuss how an integrated control package for schistosomiasis should fit within a larger integrated health package for rural and remote villages in the developing world. A holistic health system approach is required to achieve sustainable control and ultimately disease elimination.

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1. Introduction

Schistosomiasis is a neglected tropical disease caused by blood flukes of the genus *Schistosoma*. It afflicts approximately 240 million individuals in the tropics and subtropics, causing roughly 70 million disability-adjusted life years.[1,2] Schistosomiasis is the third most devastating tropical disease globally and is a major cause of morbidity and mortality in Africa, South America, the Caribbean, the Middle East, and Asia. [1,2] More than 78 countries are affected, and nearly 800 million people are exposed to the disease.[1,2]

We are presently conducting a clinical trial in Northern Samar, the Philippines, on the integrated control of schistosomiasis.[3] During the course of the trial, we have been treating patients with a single oral dose of 40 mg/kg PZQ, but noted rapid reinfection rates in an area of moderate zoonotic transmission. In the Philippines, the National Department of Health is utilizing a single oral dose of 40 mg/kg of PZQ to treat endemic communities empirically for schistosomiasis, during annual mass drug administration (MDA) campaigns. This approach has been endorsed and advocated by the WHO for the global control of schistosomiasis.[4] However, this strategy is not working due to poor drug coverage, poor drug compliance, and many other factors.[5] We discuss the many practical issues related to this global strategy and advocate for an integrated control program targeting the life cycle and the most at risk. Moreover, we discuss in detail the practical steps required to achieve sustainable control.

2. Current Global Strategy–MDA with single oral dose of 40 mg/kg of PZQ

Numerous studies have claimed that 'preventive chemotherapy' utilising 40 mg/kg of PZQ given annually can significantly reduce the prevalence and intensity of infection, and control morbidity in the long term.[6,7] However, PZQ is not 100% curative in killing adult worms, cannot kill migrating schistosomulae or the early stages of the disease, and does not prevent reinfection.[8,9] It has been stated that MDA may reduce population immunity in the long term and if stopped can lead to large rebounds in egg counts.[10,11] Moreover, multiple rounds of MDA among school children have resulted in a reduced efficacy of PZQ which poses a threat to global MDA programs.[12]

Parasitological cure depends on the treatment dose. In the early 1980s and again in 2011, WHO, in an attempt to optimize PZQ use for the treatment of schistsomiasis, launched a series of multi-country trials, comparing the efficacy and safety of 40 mg/kg versus 60 mg/kg in schistosome infected patients in Asia, Africa and the Americas.[13] In these clinical trials, the 40 mg/kg dose was found to be effective (92% cure rate) and better tolerated than the higher 60 mg/kg dose.[13] However, a recent systematic review and meta-analysis of 52 clinical trials showed that, when compared with placebo, a dosage of 30-60 mg/kg PZQ produced a cure rate of 76% (range from 67-83%) for human schistosomiasis.[14] No significant differences in cure rates were found among subjects infected with *S. haematobium*, *S. japonicum* or *S. mansoni*. The cure rate of the drug at 40 mg/kg (which is the current dose recommended by the WHO) was 52% (range from 49-55%), compared with 91% (range from 88%-92%) when dosages were increased to 60, 80, 100 mg/kg, divided into two or more doses.[14] A recent pharmacokinetic study, on a paediatric population in Africa, has recommended a higher dosage (>60 mg/kg) to achieve therapeutic cure in young children.[15]

Inadequate treatment coverage is a serious obstacle for MDA implementation. In 2001, the 54th World Health Assembly

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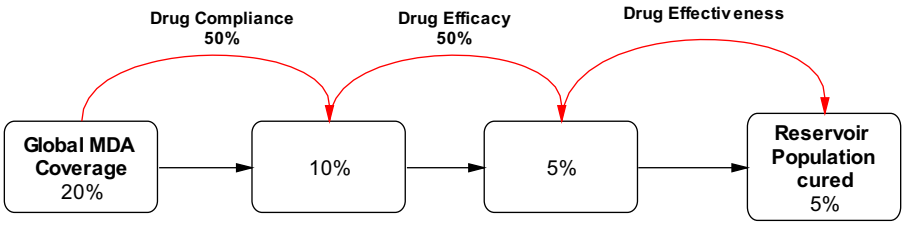

Figure 1. Percentage of global target population reached with 'preventive chemotherapy' for schistosomiasis control. The WHO reported that the global MDA coverage was approximately 20% in 2014.[17] It is assumed the compliance to free treatment is 50% and that the efficacy of PZQ at the single oral dose of 40 mg/kg is 50%.[14]

officially endorsed chemotherapy as the key public health strategy to combat schistosomiasis with the goal of achieving a drug coverage rate of 75-100% among school-aged children at risk of morbidity by 2010.[7,16] However, the target coverage was not attained according to the 65th World Health Assembly[7,16] In 2014, the global coverage was reported to be 20.74%.[17] Clearly such a coverage rate will not halt the transmission of the disease or lead to disease elimination (Figure 1). Much has been written about the benefits of MDA in order to secure large amounts of donor funding, but the operationalization of such programs has been grossly underestimated. In some of the poorest countries in the world, where MDA is taking place, the health systems are weak, understaffed and poorly resourced.[16,17] Is it, therefore, realistic to expect such countries to achieve >75% drug coverage rates? Most donors are willing to donate the drugs but few are willing to ensure safe delivery and consumption (e.g. directly observed treatment - DOT). Unless we do a better job 'on the ground' with the coordination of local control activities this strategy will surely falter. WHO and international agencies must take a more active role in operational management of MDA delivery.

Low patient compliance for free medication is another MDA impediment. Drug compliance is very low with many countries reporting <50% compliance.[5,17] It has been reported that up to 80% of those who ultimately take the drug suffer from transient side-effects such as dizziness, syncope, vomiting and diarrhoea.[5] Once the side-effects are observed and reported by others in the community, compliance quickly drops. Again if treatment is left in the hands of local untrained medical staff, compliance will surely reduce. Many of the current MDA programs in Africa utilise unpaid volunteers with no health background to deliver MDA to patients for schistosomiasis.[5,17] If such a person came to your door, would you take a drug from someone you do not know, who is untrained, for a disease you are not familiar with, with no confirmation of your infection status? Clearly not, thus the poor compliance rate globally. Getting the drugs from the pharmaceutical industry is one issue, but ensuring safe delivery and consumption is another issue, that to date has been grossly underestimated and uncoordinated.[17] The reported coverage and compliance rates are questionable given they are derived from internal evaluation reports. International and national control teams involved in MDA campaigns are under enormous pressure to show tangible results for the millions of dollars invested. Thus, they are clearly biased in the reporting of their coverage rates. Moreover, there is typically a mismatch in what is reported by the service providers for successful treatment (coverage) and who actually swallows the drug (compliance). It is well known that many who are offered the drug (e.g. put in their hands or mouth) simply throw it away or keep for later use when they feel sick. Moreover, it is not uncommon for service providers to rely on family members to administer drugs to their relatives who miss the MDA.

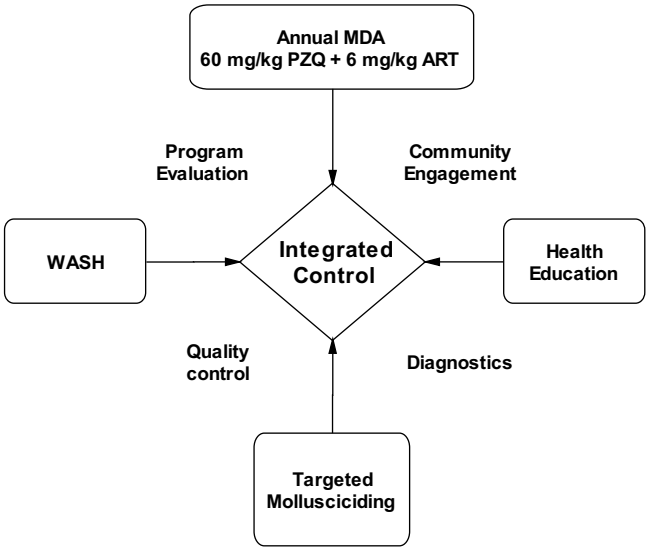

Figure 2. Key elements of an integrated control strategy required for the global sustainable control of schistosomiasis leading to disease elimination. Note: PZQ = praziquantel; ART = artemether.

3. New global strategy–split oral dose of 60 mg/kg PZQ + integrated control

What is the new global strategy based on? The new global strategy is not based on theoretical modelling but on our practical firsthand experience in participating in field-based schistosomiasis control programs over the past thirty years. What is outlined can only be achieved if members of the core control team (e.g., national and international healthcare providers) are committed to live and work in the endemic area for extended periods of time (months). On the ground planning, coordination, and daily supervision are vital to ensure local support, community engagement, drug coverage and patient compliance.[5] Key elements of the integrated control strategy required to achieve disease elimination are illustrated in Figure 2. There are two major transmission pathways in the schistosome life cycle that can be targeted by control programs: the parasites' path from humans (the definitive hosts) to snails (the intermediate hosts), and their path from snails to humans.[18] Mass PZQ treatment acts only on the transmission pathway from humans to snails and only for as long as treatment is given. A multifaceted integrated approach targets both pathways: complementing treatment with snail control, health education and water, sanitation and hygiene (WASH).

3.1. Target population

Who should be targeted for integrated control? Presently MDA campaigns are largely given to school children.[7] The advantage of this strategy is that a segment of the at-risk population can easily be reached for annual mass treatment. The disadvantage is that remote communities, and other at-risk populations are largely left untreated.[7] Given the clumped distribution of the disease these 'wormy' individuals are responsible for continued transmission. Thus, 'preventive chemotherapy' has limited impact on reducing the reservoir of infection. Future control efforts need to focus on

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