Schistosomiasis elimination: lessons from the past guide the future

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Schistosomiasis is a major neglected tropical disease, with more than 200 million people infected and close to 800 million at risk. The disease burden is estimated to exceed 70 million disability-adjusted life-years. The anthelmintic drug praziquantel is highly effective in killing adult schistosome worms, but it is unable to kill developing schistosomes and so does not prevent reinfection. As a result, current praziquantel-based control programmes in Asia and sub-Saharan Africa are not effective or sustainable in the long term. The control of neglected tropical diseases, including schistosomiasis, is a funding priority for several donor agencies, with over US$350 million committed until 2013. Here we put forward an argument that donor funds would be more effectively spent on the development of a multi-faceted, integrated control programme, which would have a greater and longer lasting effect on disease transmission than the current chemotherapy-based programmes. The development of a transmission-blocking vaccine is also of great importance. A multi-faceted integrated control programme that incorporates a vaccine, even if only partly effective, has the potential to eliminate schistosomiasis. This integrated-approach model has the potential to improve the health of a billion of the world's poorest people and its effect cannot be underestimated.

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Introduction

Schistosomiasis is a major neglected tropical disease. Over 200 million people are infected and close to 800 million are at risk.[1] This disease of poverty has proved difficult to control for centuries. Consequently, the current schistosomiasis disease burden remains high and could exceed 70 million disability-adjusted life-years.[2,3] The anthelmintic drug praziquantel, discovered in the mid-1970s, has been the cornerstone of schistosomiasis control.[4] In the 1980s, a schistosomiasis control programme in Mali funded by the German Agency for Technical Cooperation succeeded in reducing disease prevalence with mass praziquantel treatment, but disease prevalence returned to baseline levels after treatment cycles were stopped.[5–7] Similarly, during the 1990s, programmes funded by the World Bank in China and the Philippines successfully reduced the prevalence of *Schistosoma japonicum*, but there are signs that disease prevalence is increasing now that the programmes have finished.[8–10]

85% of all schistosomiasis cases occur in sub-Saharan Africa (figure 1), but until 2002, and the introduction of the Schistosomiasis Control Initiative, only sporadic control activities had taken place there.[11–13] The high cost of praziquantel and the priority given by funding bodies to other diseases, such as malaria, tuberculosis, and HIV/AIDS, were among the main reasons for this neglect. However, in the past 5–10 years, because of a renewed interest in neglected tropical diseases[14–16] and a reduction in the cost of praziquantel, there has been increased funding available for schistosomiasis control. Here we discuss past and present challenges, and propose a strategy that could potentially lead to worldwide elimination of schistosomiasis.

Drug-based control: past and present challenges

Praziquantel is highly effective in killing adult worms of all schistosome species that infect human beings[4] and, when given to people with schistosomiasis, controls morbidity well. However, because praziquantel does not kill immature schistosomes and cannot prevent reinfection, praziquantel-based control programmes have only a temporary effect on transmission and are limited in their potential to interrupt disease transmission in the long term.[17] In endemic areas, once mass treatment with praziquantel is stopped, disease prevalence can return to baseline levels within 18–24 months.[4,7,18] Less well known, but pertinent for control programme design, is the evidence for severe rebound morbidity when chemotherapy campaigns are interrupted.[18–22] When mass chemotherapy is interrupted in areas of high transmission, 80% of children have recurrent aggressive inflammation and require frequent praziquantel treatment, otherwise their morbidity would be more severe than before the mass chemotherapy campaign began.[19–21]

Evidence from Burkina Faso and Niger, where control programmes have focused primarily on mass praziquantel treatment, points to unacceptably high prevalences in high-transmission areas despite extensive donor support.[23,24] These outcomes recall the failed attempt to control schistosomiasis in Mali despite almost a decade of mass chemotherapy.[5–7] Clearly, the approach based on mass praziquantel treatment needs to be carefully scrutinised in terms of effectiveness and long-term sustainability.

The Schistosomiasis Control Initiative has been very successful in establishing national schistosomiasis control programmes and intends to reduce prevalence and morbidity in six countries in sub-Saharan Africa (Burkina Faso, Mali, Niger, Uganda, Tanzania, and Zambia). The initiative, however, primarily uses vertical mass drug distribution,[13,24] which has proved unsuccessful in the past.[5–7] Furthermore, coverage has been somewhat ineffective. Infants and preschool children are not treated and less than 50% of the high-risk population receive praziquantel, but, paradoxically, many uninfected

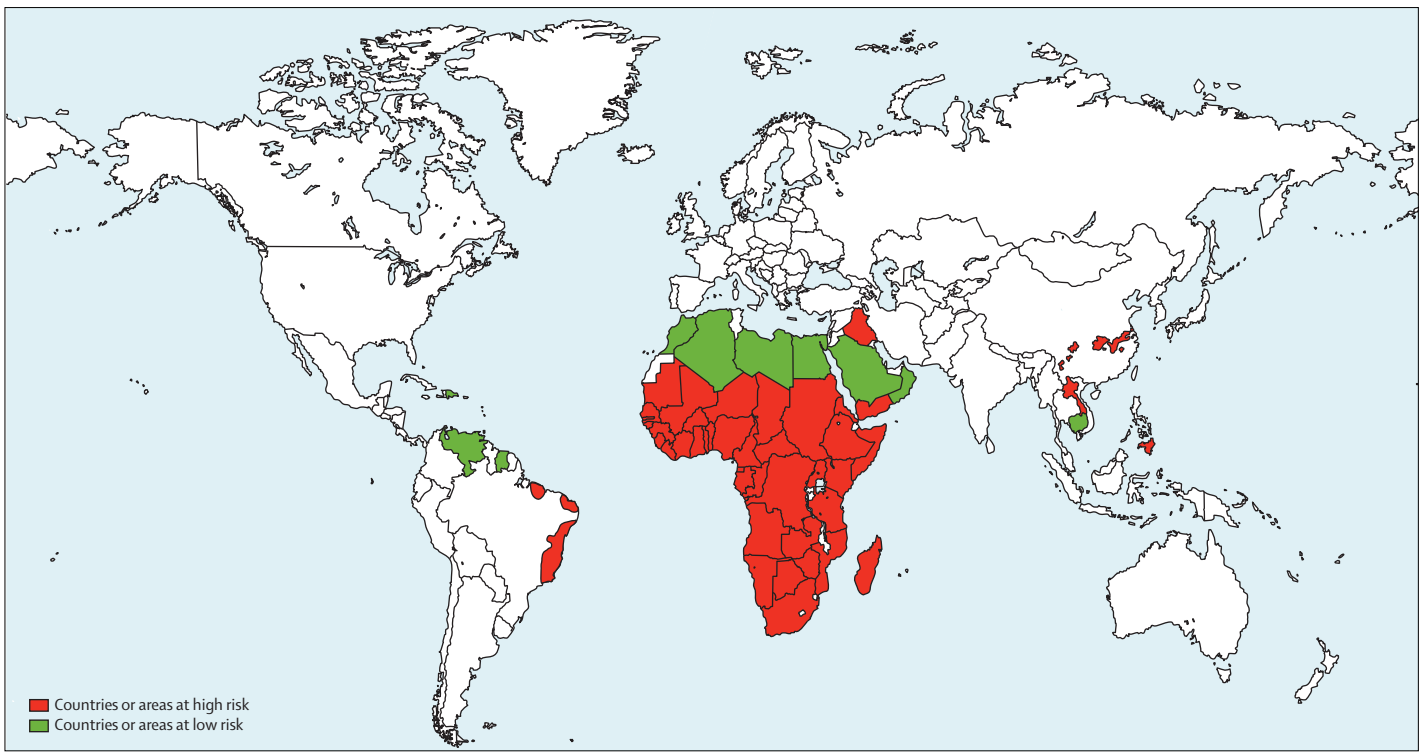

Figure 1: **Countries or areas at risk for schistosomiasis**

individuals are unnecessarily given the drug.[13,25,26] This is because of an approach that sets out to treat everyone rather than focusing on case finding and targeted chemotherapy. As a result, the overall reduction in morbidity has been small and there has been limited interruption of disease transmission. Poor compliance is also an issue; in China and the Philippines, compliance declines substantially over prolonged chemotherapy campaigns.[27,28] In light of these shortcomings, mass chemotherapy control programmes seem to be not cost effective and, more importantly, only sustainable with continued donor support.[12,29]

Thus far, roughly US$150 million has been spent on drug-based morbidity control for schistosomiasis and other neglected tropical diseases in sub-Saharan Africa.[19,30,] This total will rise to $350 million by 2013 after the USA announced an increase in funding for a new global initiative to combat neglected tropical diseases and an increase in the number of targeted countries.[19] Roughly 1·2 billion praziquantel tablets will be needed to treat 400 million people per year in sub-Saharan Africa for at least 5 years, at an annual cost of US$100 million.[26,31] Countries in sub-Saharan Africa are among the poorest in the world, with roughly 73% of the population living on less than US$2 per day.[32] Without continuing financial support, these countries will be unable to finance and sustain mass treatment programmes against schistosomiasis or any of the other neglected tropical diseases.[23] The crucial question, especially in times of global economic uncertainty, is what will happen to the current neglected tropical disease control programmes if donor funding stops?

Future integrated, sustainable control

Important and urgent decisions must be made on the future approach needed for effective, sustainable control and elimination of schistosomiasis. The strategy used over the past 25 years in sub-Saharan Africa focuses on short-term morbidity control.[5–7,13] Because transmission reduction is an important step towards elimination, a control programme that controls morbidity and reduces transmission would be more cost effective because it would not incur the cost of continually treating new infections. Such an approach is being used effectively in China.[33–37] Control and elimination of neglected tropical diseases do not involve treatment of the disease alone: many people with neglected tropical diseases are at the mercy of inadequate health and social systems that need to be improved if any long-term benefit is to be achieved.

There are two major transmission pathways in the schistosome life cycle that can be targeted by control programmes: the parasites' path from human beings (the definitive hosts) to snails (the intermediate hosts), and their path from snails to human beings (figure 2).[34] Mass praziquantel treatment acts only on the transmission pathway from human being to snail and only for as long as treatment is given. By combining chemotherapy with known and effective control measures, such as the use of

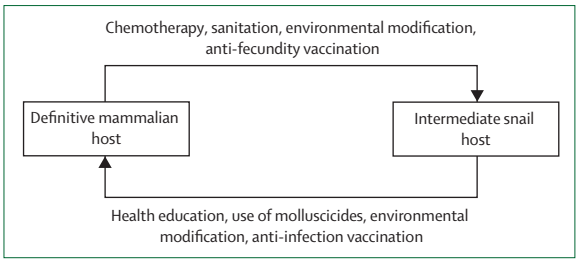

Figure 2: **Interventions that can target transmission pathways in the schistosome life cycle**

molluscicides, environmental modification, improved sanitation, and health education, multifaceted integrated control programmes can target both transmission pathways. Such effective use of donor money could result in the reduction and even elimination of schistosomiasis from endemic areas.

Because of the focal nature of schistosome transmission, the multifaceted integrated control programme we are advocating would build on historical and current data, and use case finding, geographic information systems, and remote sensing to develop predictive maps that would allow endemic areas and re-emerging pockets of transmission to be targeted.[38,39] Our approach would be tailored to specific endemic settings and be incorporated into national and local health services. This integrated approach is being used with success in China, where the elimination of schistosomiasis is regarded as one of the top public-health priorities along with HIV/AIDS, tuberculosis, and hepatitis B.[40] The challenge in sub-Saharan Africa and other parts of Asia is to develop a sustainable, multiple component schistosomiasis control strategy that is cost effective, and more importantly, not dependent on endless donor funding. Systemic integrated approaches to control communicable diseases, such as malaria, tuberculosis, and HIV/AIDS, are proving successful in sub-Saharan Africa,[41] and although an integrated strategy might initially be more expensive than a chemotherapy-based approach, a greater and longer-lasting effect on transmission makes it more cost effective and sustainable in the long term.

Vaccines are thought of as silver bullets for public health interventions in the control of infectious diseases; their crucial role in the eradication of smallpox in 1978 substantiates this notion.[42] The recent publication of the *Schistosoma mansoni*[43] and *S japonicum*[44] genomes takes us a step closer to the identification of key protective molecules and the development and implementation of effective antischistosome vaccines, although many research questions need to be addressed if we are to successfully achieve this goal.[45] Schistosomiasis japonica, caused by *S japonicum,* is a zoonosis, and in countries, such as China and the Philippines, where animals are major reservoirs for this disease, a transmission-blocking vaccine for livestock would be beneficial and would probably take less time to develop than a human vaccine.[34] In China, randomised, double-blind trials of two DNA vaccines for water buffaloes, encoding well researched *S japonicum* antigens, reduced worm burden, fecal egg counts, and miracidal hatching by roughly 50%.[46] Mathematical modelling predicts that these vaccines, in combination with other control options, will substantially reduce transmission, meaning that a transmission-blocking bovine vaccine could well be available within the next few years.[46–48] Vaccine development should be a priority along with other avenues of schistosomiasis research, including the search for alternative drugs to praziquantel, because resistance against the drug in the future cannot be ruled out.

We believe that multiple component, integrated control programmes incorporating praziquantel treatment with transmission reduction through other control measures, such as use of molluscicides, environmental modification, health education and promotion, and improved sanitation, is the best option for schistosomiasis control. Even if only partly effective, anti-schistosome vaccines, incorporated as part of an integrated control strategy, will be needed to accelerate efforts to eliminate a disease that has existed for at least two millennia.[19] This integrated-approach model has the potential to improve the health of a billion of the world's poorest people and its effect cannot and should not be underestimated.

Contributors

DJG, AGR, and DPM had the idea for and prepared the paper. YL, GMW, and RB assisted with the preparation of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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