A randomised controlled clinical trial on the safety of co-administration of albendazole, ivermectin and praziquantel in infected schoolchildren in Uganda

Introduction
Parasitic helminth infections, including lymphatic filariasis (LF), schistosomiasis and soil-transmitted helminthiasis (STH), are prevalent and often co-exist among poor populations in the developing world. Schistosomiasis and STH have particularly high prevalence among school-aged children, and LF is also more prevalent in this population than previously thought. Ivermectin (IVM) and albendazole (ALB) are used in combination to treat LF; praziquantel (PZQ) is used to treat schistosomiasis; and ALB (or mebendazole) is used to treat STH. These drugs are delivered separately in two drug packages (IVM+ALB and PZQ±ALB) in the current integrated national control programs on the neglected tropical diseases (NTDs). Considering the co-endemicity of these three diseases, combining treatment for simultaneous control of these diseases using a single-dose drug package would minimize costs and increase coverage. Single-dose combination treatment is believed to increase patient adherence, prove less difficult in terms of distribution and be more cost effective. The aim of the study was therefore to test the safety of co-administration of ALB, IVM and PZQ as a single-dose package in the treatment of children aged 5-18 with various infection statuses with LF, schistosomiasis and STH.

Methods
The study was conducted in Kei subcounty, Yumbe District, which was chosen because it had the highest prevalence of triple infection in Northern Uganda. The study sample consisted of children between the ages of 5-18 from 9 schools. A sample of around 50 children was randomly selected for each infection status (48 with LF alone, 60 with schistosomiasis alone, 41 with STH alone, 49 with LF + schistosomiasis and 37 with LF + schistosomiasis + STH) from the total available children for all infectious statuses except STH alone and LF + schistosomiasis + STH, for which the limited number of students meant they were all enrolled in the study. Participants were randomized to the test group or control group for each infection status. The test groups were given a single-dose drug package (ALB+IVM+PZQ), in comparison to the control groups which were treated according to the current treatment regimen specific to each infection status in the integrated NTD control program. All children were given food prior to treatment. Post-treatment, a pediatrician blinded to the treatment regimens monitored the potential adverse drug reactions (ADR) and serious adverse effects (SAEs) in all children for 7 days. All relevant symptoms were recorded at baseline to ensure that symptoms reported after drug administration were due to the treatment. The efficacy of different regimens was also monitored.
Results
There were 235 schoolchildren enrolled in the study: 118 in the test groups and 117 in the control groups. After 13 children were lost to follow-up, the remaining children (n=222, 130 boys and 92 girls) were treated as follows: 115 in the test groups and 107 in the control groups. Among the participants, 69.9% had light, 24% had moderate and 6.2% had heavy infection with schistosomiasis; all STH infections were light; and in 53 children with LF worm density data, 75.5% had 1-200 microfilariae and 24.5% had 201-1500 microfilariae per µl of blood. The study found no statistically significant differences between the reported ADRs among the test and control groups over the 7-day follow-up period after treatment. No children reported SAEs or serious ADRs following treatment. Percentage reduction of microfilariae and egg counts after treatment was comparable in both groups. There were no statistically significant differences in the mean intensity of infection between the test and control groups in any of the infection status groups.

Discussion
Co-administration of ALB, IVM and PZQ in the treatment of children aged 5-18 co-infected with LF, schistosomiasis and STH was safe among the participants in this study. Children treated with triple combination therapy did not experience more ADRs than those treated with the current NTD program regimen specific to each infection status. ADRs, for example difficulty in breathing, diarrhea, vomiting and blood in stool, constitute one reason for low MDA (mass drug administration) compliance. Therefore, though the incidence of ADRs may not decrease, treating for all three diseases on one occasion means that persons treated will experience side effects, if any, only once rather than each time they get treatment. This may address the issue of persons declining further treatment after experiencing ADRs the first time, thereby increasing treatment coverage. As the reduction in mean intensity was the same among those receiving triple combination therapy and the conventional regimens, the study results also indicate that combined therapy is equally efficacious. Study limitations include the fact that the sample size was relatively small and the follow-up period was quite short.

Editor’s Comments
The purpose of integration of the NTD control programs is to reduce the costs and increase the coverage of the national control programs, taking advantage of the available effective drugs. The current integrated NTD control programs through MDA are targeting five major NTDs according to the World Health Organization preventive chemotherapy guidelines. In the national integrated NTD control programs currently being implemented, the drugs used for the five targeted diseases are normally distributed in three separate packages (ALB+IVM, PZQ±ALB, and Zithromax®) with short intervals in between. This reduces the possibility of cost reduction and increases the possibility of decreased MDA compliance. The current study combined ALB, IVM and PZQ as a single-dose drug package for LF, schistosomiasis and STH, and showed that this combined package was as safe and efficacious as the normal drug regimens in school children with prior MDA activities. Such drug combination has also been used in Nigeria and in Zanzibar in the control projects. In addition, the International Trachoma Initiative has recently supported a study in Mali on the safety of the combination of Zithromax® for trachoma with LF treatment. Therefore, such studies are important in illustrating the safety and efficacy of combining multiple drugs in
MDA, and have the potential to improve the cost-effectiveness in the integrated NTD control programs. However, precautions must be taken to expand such multi-drug packages to large-scale use in the national NTD control programs. Adoption of such drug combinations should be considered carefully according to the local context. More in-depth training of community drug distributors should be given to avoid confusion by drug distributors as multiple drugs and multiple dose-poles are involved. More stringent monitoring mechanism for side-effects need to be in place. In endemic areas without prior MDA activities or with very high level intensity of multiple infections, such single-dose drug package for multiple NTDs may not be used at the beginning of the program, and further studies in such areas are needed.

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