Safe mass drug administration for neglected tropical diseases

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The use of mass drug administration for the control of diseases dates back to the early 1900s, with campaigns for the control of soil-transmitted helminths in the USA,[1] and worldwide malaria eradication attempts for more than 70 years.[2] However, mass drug administration for neglected tropical diseases gained particular prominence in the 1990s. Diseases such as onchocerciasis, lymphatic filariasis, trachoma, schistosomiasis, and soil-transmitted helminths are amenable to mass treatment and control as a result of the availability of safe and affordable drugs.[3] These neglected diseases also tend to overlap in their geographical distribution, typically affecting the poorest of the poor, and therefore concomitant administration of free or low-cost drugs against multiple neglected tropical diseases has been recommended to optimise the use of resources, save operational costs, and increase the impact of health interventions. Nonetheless, co-administration of multiple drugs requires for rigorous assessments of safety and drug interactions.

In their Article[4] in *The Lancet Global Health*, Lucia Romani and colleagues evaluate the feasibility and safety of azithromycin and ivermectin co-administered through mass drug administration for the treatment of trachoma and scabies on the Solomon Islands. The investigators used a prospective, single-arm, before-and-after community intervention methodology, and they evaluated the safety and coverage of mass drug administration regimens for scabies and trachoma separately, as well as the co-administration for both diseases. No severe adverse events were reported in a population of more than 21 000 individuals who received both azithromycin and ivermectin, and mild adverse events resolving within 1 week were reported by 2·6% of the population assessed, similar to historic rates observed after administration of the drugs alone. High treatment coverage was also reported—of the enrolled population of 26 188 individuals, 25 488 [97·3%] received the trachoma regimen and the first dose of the scabies regimen, and 21 817 [85·6%] received the trachoma regimen and both doses of the scabies regimen—indicating feasibility of co-administration of both drugs. This study represents the first large-scale evaluation of this combination, providing evidence for its safety. Despite the limitations of this study (particularly the inability to use randomised trial methodology and the duration between drug administration and assessment of adverse events), this study provides evidence for the use of safe drug combinations in the control of neglected tropical diseases and shows the feasibility of large-scale evaluation of combination mass drug administration.

Safety is a pivotal issue in combination mass drug administration, where (unexpected) interactions can occur at multiple levels, requiring large-scale studies such as the one conducted by Romani and colleagues to detect rare severe adverse events and increased frequency of adverse events. First, drug–drug interactions can occur on a pharmacokinetic level resulting in increased (or decreased) exposure to any of the combined drugs. This outcome was actually demonstrated for the co-administration of ivermectin and azithromycin in healthy volunteers, where bioavailability of ivermectin was increased by 37% in a large subset of participants when co-administered together with azithromycin.[5] The increased ivermectin exposure was nevertheless still considered safe,[5] which is supported by Romani and colleagues' findings. In fact, this drug–drug interaction might actually partly benefit efficacy of ivermectin. Second, drug–drug interactions can also occur on a pharmacodynamic level, with side-effects potentiated by synergy or summation of the toxicological effects of the co-administered drugs; however, on the basis of the reported frequency of adverse events in Romani and colleagues' study, this interaction probably did not occur despite similar adverse events for both drugs in monotherapy. Third, interactions can even occur between the drug and pathogens in the patient population, resulting in unwanted effects. For instance, ivermectin administration in patients co-infected with *Loa loa* can result in severe life-threatening encephalopathies as a result of an inflammatory response associated with massive microfilariae antigen release.[6] This interaction underlines that extrapolation of acceptable safety outcomes, such as from this study, to other populations and geographical settings remains difficult and should be done with caution, mechanistic insight, and proper pharmacovigilance.

Positive findings from evaluations of a combination regimen including ivermectin, diethylcarbamazine, and albendazole for the treatment of lymphatic filariasis have led to adoption of this regimen by WHO.[7] Further implementation of azithromycin into this regimen could potentially also target trachoma, scabies, and yaws, thus strengthening the case for integration of interventions for neglected tropical diseases. Combination treatments, however, need to be carefully implemented, with assessments to ensure that the diseases being targeted do not overlap with other diseases for which any of the drugs pose potential health threats. For example, although azithromycin and ivermectin co-administration could be implemented in many areas of Africa, other combination treatments are required in areas where trachoma and scabies overlap with *L loa*. Alternatively, other implementation strategies may be considered (eg, test-and-not-treat approaches using innovative point-of-care screening tools).[8] Thus, strict safeguards must be ensured and monitored by capable regulatory and implementation authorities. The potential effect of azithromycin drug combinations on the development of antibiotic resistance would need to be monitored,[9,10] given its use in the treatment of other infections such as gonorrhoea. Finally, cost-effectiveness studies will help strengthen the argument for wider public health acceptability and implementation.

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We declare no competing interests.

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