The contribution of mass drug administration to global health: past, present and future

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Mass drug administration (MDA) is a means of delivering safe and inexpensive essential medicines based on the principles of preventive chemotherapy, where populations or sub-populations are offered treatment without individual diagnosis. High-coverage MDA in endemic areas aims to prevent and alleviate symptoms and morbidity on the one hand and can reduce transmission on the other, together improving global health. MDA is the recommended strategy of the World Health Organisation to control or eliminate several neglected tropical diseases (NTDs). More than 700 million people now receive these essential NTD medicines annually. The combined cost of integrated NTD MDA has been calculated to be in the order of $0.50 per person per year. Activities have recently been expanded due, in part, to the proposed attempt to eliminate certain NTDs in the coming two decades. More than 1.9 billion people need to receive MDA annually across several years if these targets are to be met. Such extensive coverage will require additional avenues of financial support, expanded monitoring and evaluation focusing on impact and drug efficacy, as well as new diagnostic tools and social science strategies to encourage adherence. MDA is a means to help reduce the burden of disease, and hence poverty, among the poorest sector of populations. It has already made significant improvements to global health and productivity and has the potential for further successes, particularly where incorporated into sanitation and education programmes. However logistical, financial and biological challenges remain.

1. Introduction

A substantial proportion of the world’s disease burden is caused by infectious agents that lead to mortality or severe morbidity among many millions of individuals. The target of achieving sustainable development and elimination of extreme poverty by the year 2015, as set by the 2000 United Nations Millennium Declaration and the ambitious eight Millennium Development Goals (MDGs; www.un.org/millenniumgoals/), dominates recent development aid strategies. As we enter the final stage, significant progress has been made to achieve the MDG 6 target, which aimed ‘to Combat HIV/AIDS, malaria and other diseases’. Such other diseases’ include the neglected tropical diseases (NTDs), a group of highly debilitating diseases caused by a range of viruses, bacteria, protozoa and helminths that infect more than one billion people, a sixth of the world’s population, but predominantly the poorest of the poor [1]. NTDs cause devastating consequences to individuals and communities, including, but not exclusive to, blindness (onchocerciasis and trachoma), hydrocele of the scrotum and/or swellings of the lower limbs or breasts (lymphatic filariasis/LF), liver and bladder fibrosis and cancer (schistosomiasis), cholangiocarcinoma or bile duct cancer (opisthorchiasis), anaemia, malnutrition and stunting (soil transmitted helminths/STHs), cutaneous and mucocutaneous lesions (leishmaniasis) and severe cutaneous erosion of the skin (Buruli ulcer).
These pathologies can progress to a stage where they are irreversible and untreated, resulting in death or lifelong disability and lack of social, educational or economic prospects for those affected and their families/carers, hence contributing to the poverty cycle. The scientific rationale for grouping these infectious agents as NTDs began in the years following the release of the MDGs and emerged through key World Health Organization (WHO) meetings held in Geneva and Berlin [2–7]. An initial assessment suggested that 14 of the major NTDs kill an estimated 534 000 people worldwide every year, while causing a disease burden measured in disability-adjusted life years (DALYs) that competed with HIV/AIDS, tuberculosis and malaria [5]. Even within this, there is significant debate and dispute over the potential underestimation of these NTD DALY figures [8]. Contributing factors include, for instance, the misclassifications of several of the NTD pathologies to cancers, hepatic, renal and neurological conditions, and the failure to attribute any burden of NTD-associated depression and mental health issues to NTD DALYS [8,9]. There remains no doubt, however, that the impact on morbidity of NTDs greatly exceeds the mortality contribution to this burden. Furthermore, the impact of NTDs on worker productivity, child development and maternal health add up to billions of dollars lost annually and therefore maintains low-income countries in poverty and traps the ‘bottom billion’ in destitution [1,10,11].

A subset of seven of these NTDs are amenable to control using annual mass drug administration (MDA) with, pre-dominantly oral, medicines: one bacterial infection, *Chlamydia trachomatis*, the causative agent of blinding trachoma, and six helminthic diseases: onchocerciasis or river blindness caused by *Onchocerca volvulus*; LF or elephantiasis caused by *Wuchereria bancrofti*, *Brugia malayi* and/or *B. timori*; schistosomiasis or bilharzia caused by four major species of *Schistosoma*: urogenital resulting from infection by *S. haematobium* and intestinal schistosomiasis mainly caused by infection with *S. mansoni*, *S. japonicum* or *S. mekongi*; and the STHs, in particular *Ascaris lumbricoides*, *Trichuris trichuria*, and hookworm caused predominantly by *Necator americanus* but also *Ancylostoma duale*role. The term preventive chemotherapy (PC) was introduced by the WHO to define the strategic approach of treating populations infected, or at risk of infection, with these NTDs without individual diagnosis [11]. MDA treatment programmes are designed explicitly to reduce or prevent morbidities in the case of STHs and schistosomiasis and/or interrupt transmission in the case of LF, trachoma and onchocerciasis, with safe and effective drugs either alone or in combination. MDA delivery is usually undertaken based on community distribution, although the approach, such as school-based, faith-based or health service organized campaigns, varies depending on the local or national conditions or policies, as well as disease endemocities.

The drugs given have different mechanisms of action and effects. Single dose albendazole (400 mg) or mebendazole (500 mg) is given primarily to pre-school (over 2 years old) or school-aged children to kill the STHs and thereby reduce STH-induced morbidities, including anaemia, growth retardation and poor intellectual and cognitive development. Albendazole or mebendazole works best for ascariasis and hookworm infection, but with a less efficient therapeutic effect for trichuriasis, suggesting the need for sometimes adding a second drug, such as ivermectin (IVM; Mectizan) or oxantel for trichuriasis, in highly endemic areas [12].

Although the precise mechanism of action is yet to be confirmed, praziquantel (PZQ) targets adult trematode worms. PZQ, administered at the standard single dose of 40 mg kg$^{-1}$, is the only currently available drug for schistosomiasis. PZQ is also efficacious against several of the food-borne trematodes, administered at single doses of between 25 and 50 mg kg$^{-1}$. Reducing infection intensities in these cases through killing the adult worms aims to prevent the development of the serious consequences of long-term infection.

At present, IVM is the only safe drug available for MDA of onchocerciasis. IVM, administered at the standard dose of 150–200 μg kg$^{-1}$, has a rapid effect on the embryonic stage of the parasite, the microfilariae (mf), which causes the ocular and cutaneous manifestations of the disease. As a result, skin microfilarial loads decrease by 95–99% within one month after treatment. The drug also aims to block the production of new mf by the adult female worms, for at least three to six months post treatment. Furthermore, IVM treatments repeated at one- to three-monthly intervals have some, though moderate, macrofilaricidal effect on the longevity of the adult worms. For LF, it is the adult worms of *W. bancrofti, B. malayi* and/or *B. timori* that directly cause the significant pathology and morbidity, rather than the microfilaria. As IVM does not kill adult filarial worms directly, the LF MDA strategy is to treat all those eligible in an endemic area for, on average, at least 6 years, although with some variability in relation to initial prevalence levels. In African countries co-endemic for both onchocerciasis and LF, IVM is co-administered with albendazole, which also has macrofilaricidal properties, providing important collateral benefits through simultaneously targeting other NTDs such as several STHs. The use of combination chemotherapy also helps forestall the evolution of potential drug resistance. An alternative LF microfilaricidal drug, diethylcarbamazine (DEC) cannot be used in Africa owing to the risk of side-effects in individuals co-infected with *O. volvulus*. DEC can cause severe Mazotti reactions, characterized by intense itching owing to the rapid death of microfilaria in the skin or potential blindness if in the eye. In Asia, however, where there is no *O. volvulus*, DEC is co-administered with albendazole by the Global Lymphatic Filariasis Elimination Programme (GPELF). Unfortunately, there are currently no MDA medicines available that are capable of killing the adult filarial worms. However, *Wolbachia* endosymbionts of both *O. volvulus* and *W. bancrofti* provide key targets because of the adult filarial worms’ dependence on these symbionts. Studies in humans have shown that the antibiotic doxycycline has a yet another effect, either killing or permanently sterilizing the female worms through killing the *Wolbachia*. At present, the duration of the required antibiotic course is four to six weeks and hence cannot be used at scale for MDA, although could be used in restricted settings under medical supervision, for example where there has been evidence of reduced efficacy of the standard anti-filarial drugs [13].

For trachoma, while blindness is irreversible once it has occurred, it can be prevented through a combination of the SAFE strategy (Surgery for trichiasis, Antibiotics to treat *C. trachomatis* infection, and Facial cleanliness and Environmental improvement to reduce transmission). Within this, WHO currently recommends two antibiotics for the control of trachoma: 1% tetracycline eye ointment and azithromycin. Tetracycline eye ointment can clear ocular *C. trachomatis* infection if administered to both eyes twice daily for six weeks. Though valuable, particularly for babies under six months, it is difficult to apply and so compliance is often poor.
Azithromycin, by contrast, clears ocular C. trachomatis infection with a single oral dose (at 20 mg kg\(^{-1}\) body weight) and is well tolerated by both children and adults.

Several of these drugs used for the major seven NTDs under target are also efficacious against other NTDs, thereby potentially broadening the impact of MDA in terms of improving global health. Azithromycin for trachoma, for example, also has beneficial effects against the skin NTD yaws, and the WHO has therefore recently added the control or elimination of yaws using azithromycin as a target [14]. Similarly, IVM used for LF and onchocerciasis control has a potent effect on reducing scabies [15], a mite infestation that can, in severe cases, result in secondary bacterial infections leading to rheumatic heart disease or glomerulonephritis.

### 2. Scaling up of neglected tropical disease mass drug administration: from past to present

MDA for the neglected diseases of neglected populations is neither an exclusively tropical nor recent phenomenon. In 1910, for instance, the Rockefeller Sanitary Commission (RSC) found that 40% of school-aged children in the deep south of the USA were infected with STHs, and in particular hookworm [16]. The RSC sponsored an anthelmintic MDA campaign, combined with sanitation and education, across the region which substantially reduced hookworm infection prevalence levels, intensities and morbidity. Moreover, areas with higher levels of hookworm infection prior to the RSC MDA control programme showed greater increases in school enrolment, attendance and literacy after the intervention, and long-term follow-ups indicated a substantial gain in income that coincided with inclusions within this hookworm MDA programme [16]. Such success in terms of the health, education and economic development of those poorest of the poor within the USA lends support in favour of the contribution of MDA to similar health and development potential across the rest of the developing and/or tropical world.

Onchocerciasis, for example, was identified as a barrier to social and economic development in the 1960s, in particular in many areas across West Africa, as a result of the high prevalence of onchocercal blindness. At that time, the use of insecticides was considered to be the only solution to reducing transmission and was the basis for the establishment of the Onchocerciasis Control Programme (OCP) [17]. Merck & Co. Inc. recognized the additional beneficial effects of annual treatment with IVM, but also that onchocerciasis afflicted the poorest individuals who could not afford even a subsidized drug and hence there was no commercial market. The decision to donate IVM by Roy Vagelos, the then CEO of Merck & Co. Inc. for ‘as long as needed in the quantities needed’ to eliminate river blindness was a landmark public health decision. Twenty-five years later few people become blind from onchocerciasis and approximately 90 million people annually receive their free dose of IVM. Onchocerciasis was also endemic in six countries in the Americas (Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela), and thus an onchocerciasis elimination programme was established in 1990 (Onchocerciasis Elimination Programme in the Americas; OEPA) with the objective of eliminating the disease throughout the region. In contrast to Africa, a strategy of twice a year IVM treatment was adopted, and to date one focus in Colombia has been certified as free of transmission [18]. The transition from the view of IVM as purely a tool to provide sustainable control to an elimination objective in Africa was based on studies in Mali and Senegal over a period of 15–17 years [19]. Following cessation of IVM treatment in five to eight villages per focus, evaluation after 16–22 months showed that no infected individuals were found and vector infectivity was less than 0.2 per 1000 blackflies, suggesting that transmission has been interrupted. Similar results have been obtained from studies in several African Programme for Onchocerciasis Control (APOC) project areas throughout Africa [20]. These results suggest that MDA with IVM alone can, if given at coverage of at least 70%, impact onchocerciasis transmission even without concurrent vector control interventions. However, other studies in Cameroon have shown evidence of ongoing transmission despite up to 17 years of MDA, suggesting IVM treatment needed to be continued and that a ‘one size fits all’ approach is rarely applicable [21].

For LF, the GPELF was initiated in the 1990s following the donation of albendazole by GlaxoSmithKline and IVM by Merck & Co. Inc. for African countries co-endemic with onchocerciasis and a World Health Assembly (WHA) resolution calling for the elimination of the disease. The programme started slowly, with only nine million people being treated through MDA in 2000. However, there has been significant progress over the past decade with more endemic countries initiating MDA programmes, and by 2011 over 500 million people globally received annual treatment. MDA control efforts have recently led to a certified national elimination of LF in Togo [22].

The International Trachoma Initiative was set up in the late 1990s by the Edna McConnell Clark Foundation. Pfizer joined the programme and agreed to donate azithromycin to eliminate blinding trachoma, as a component of the SAFE strategy. By 2002, these programmes were expanding, helped by additional funding from the Bill and Melinda Gates Foundation. An estimated 325 million people are at risk of trachoma in 53 countries. Current estimates suggest that 21 million require treatment, 7.2 million require surgery and over a million people are irreversibly blind, the majority of whom are within sub-Saharan Africa (SSA). In 2011, WHO reported that 52 million doses of azithromycin were provided through MDA [23].

For schistosomiasis, control measures have included a combination of drug treatment, improved sanitation and mollusciciding, with some enhanced education components. Of these, snail control was once thought to be the answer, but after development of PZQ in the 1970s chemotherapy has emerged as the major tool. China was recognized for having an intensive and comprehensive control programme, by combining the destruction of the amphibious snails with treatment of infected humans and selected bovine animal hosts using locally produced PZQ [24,25]. The Philippine schistosomiasis control programme used similar techniques to China, and both programmes were funded by World Bank loans [26]. Brazil originally based their control on the drug oxamniquine, but after 1996 both oxamniquine and PZQ were used for MDA in endemic areas [27]. Egypt has achieved success with their programme which started in 1988, again with World Bank support, enabling extensive use of locally formulated PZQ. Initially only diagnosed infected cases were treated, but since 1996 MDA has been deployed in schools and communities. Egypt’s extended programme had a major impact on the prevalence of, and morbidity due to, schistosomiasis [28]. Prior to 2002, there
was, however, no additional national schistosomiasis control programme in operation in SSA [29,30]. In 2002, the ‘Schistosomiasis Control Initiative’ (SCI) was established at Imperial College with funding from the Bill and Melinda Gates Foundation to support an initial six countries to implement control programmes [31]. SCI immediately combined PZQ delivery with albendazole or mebendazole for integrated STH control. Over the first 10 years, SCI has assisted the countries to deliver over 100 million PZQ treatments against schistosomiasis and many more STH treatments, with significant improvement on both child and adult health as a consequence [31–34]. Goals to eliminate schistosomiasis have also been recently articulated by the WHO [35] and the London Declaration of the NTD coalition, with signatories pledging to contribute towards the control or elimination of 10 NTDs by the end of the decade (2020). The NTD community, however, appears to be divided on whether it is feasible to eliminate schistosomiasis using MDA alone or whether other measures and technologies will be required [36]. The suggestion for developing anthelminthic vaccines to be used to complement chemotherapy has also been made for both STHs and schistosomiasis [37,38]. However, the feasibility of this in the timescale required, notwithstanding the problems of financing and delivery, suggest that vaccines may not be the panacea many advocate, particularly given that there are a few anti-parasite vaccines even for parasites of animal health importance.

The progress of each of these individual MDA programmes over the past decade has been impressive, with already over 700 million NTD treatments given annually by 2013 [39]. Furthermore, following a series of policy documents identifying the geographical overlap between the major NTDs, high rates of co-infections, and opportunities to link MDA programmes [2–4,6,7]. Integrated NTD control initiatives became the main pillar of delivery of MDA to treat and control the seven major human NTDs simultaneously. Such programmes have been given further momentum following the London Declaration on NTDs of 30 January 2012 and then a 2013 WHA resolution for integrated NTD control and, in certain cases, elimination. The ministries of health in the developing countries have become more aware and receptive to act. The expansion of MDA is underpinned through generous drug donations, all of which are now designated as essential medicines by the WHO. The value of these donations has been estimated to be between US$2 and 3 billion annually [40]. National programmes of integrated NTD MDA are now underway in more than 70 countries. These programmes are led by health ministries of disease endemic countries, often with key technical assistance to deliver these drugs from public–private partnerships such as the SCI, RTI (Research Triangle International), HKI (Helen Keller International), Sight Savers, CBM (Christian Blindness Mission), the Carter Center, and others. The WHO, and its regional offices, has played a key leadership role in setting strategy, publishing guidelines and providing technical assistance to countries and global advocacy in support of a diverse group of partnerships. Through the support of the United States Agency for International Development (USAID) NTD Program, NTD programmes are underway in 20 countries in Africa and Asia, as well as in Haiti. USAID has also set key elimination targets for LF and blinding trachoma by 2020, and the elimination of onchocerciasis in the Americas by 2015. Similarly in 2009, the UK Department for International Development (DFID) expanded its commitment to match USAID-supported activities, working through public–private partnerships such as the SCI, Global Alliance for LF (Liverpool School of Tropical Medicine) and APOC, across SSA and the Yemen. These integrated NTD control programmes were predicted to cost between US$0.40 and $0.50 per person annually [2,7] and recent analyses have confirmed the accuracy of these initial estimates [41]. Indeed for some countries, such as Niger, costs as low as US$0.19 [42] have been reported. These costs represent only a small proportion of the total government expenditures on health, even for the least well-resourced health systems [43].

3. Future

One-sixth of the human population is infected with one or more NTDs and we have the safe and affordable essential medicines to treat many of these. In 2011, an estimated 1.41 billion people required MDA for LF, 127 million people for onchocerciasis, 243 million for schistosomiasis, 873 million for STH infections and 281 million for trachoma [23,38]. Between 2011 and 2013, over 700 million people received annual MDA treatments annually [39,44,45]. This number represents approximately 37% of the 1.902 billion people in 125 countries who require annual MDA, of which 22% require MDA for two diseases and 33% for at least three geographically overlapping NTDs [38,44,45]. These questions are therefore why have these NTDs not been controlled to date and why are so many people still untreated? Perhaps the ultimate question is whether the aim of NTD elimination is ever possible. There are many reasons for the continued persistence of these NTDs: (i) one is simply that those infected and affected are among the poorest of the poor—with ‘no voice and no wealth’ and often not served well with health facilities and/or in conflict or post-conflict countries; (ii) the drugs available are also, in some cases, relatively new, with, for example, IVM since 1987, PZQ since 1988, other drugs even more recent, and the international drive to implement MDA newer still; (iii) despite the evidence for the cost-effectiveness, global health policy-makers have not prioritized NTD control as much as other global health interventions for diseases such as HIV/AIDS or malaria; (iv) NTDs are chronic infections and any disease control programme less than 100% effective will take time to have an impact at the population or global health level; and finally (v) we must not underestimate the challenge of the parasites and pathogens themselves, their ability to adapt and evolve and hence maximize their own fitness whatever control programme measures we present them with [46–48].

As regards points (i)–(iii), the future looks encouraging, but it is by no means assured. In January 2012, a group of partners, including DFID, USAID, the Bill and Melinda Gates Foundation, the WHO, the World Bank and major pharmaceutical companies, made commitments to sustain and expand NTD programmes to control or eliminate 10 NTDs by 2020 (www.unitingtocombatntds.org). The recent report chaired by David Cameron and the presidents of Liberia and Indonesia to the UN Secretary General on the post-2015 development agenda has placed NTDs for the first time as a health target [49], a huge paradigm change in health policy thinking. By 2014, some 700 million annual treatments should be delivered against LF, 100 million against onchocerciasis, over 70 million against
Table 1. Biological factors for and against the potential evolution and/or establishment of drug resistance in the major NTDs.

<table>
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| No evidence of drug resistance emerging after long-term MDA in some situations  
  e.g. *S. japonicum* in China [51],  
  e.g. trachoma in Tanzania [52] | Resistance has evolved to all the veterinary anthelmintics  
  Many NTD MDA programmes reliant on a single drug,  
  e.g. IVM for onchocerciasis, PZQ for schistosomes  
  *S. mansoni* evolved resistance to the previous major drug oxamniquine [53–58]  
  Can select for drug resistance in animal experimental models, e.g. PZQ in *S. mansoni* [53]  
  Limited molecular markers available/lack of mechanistic knowledge of drug action on some NTDs, e.g. PZQ  
  Limited or no systematic monitoring and evaluation for drug efficacy within MDA programmes  
  Existence of resistance appears on a sigmoidal curve—once detected often too late to react  
  Variation in drug sensitivities in natural parasite populations upon which selection can act,  
  e.g. *S. mansoni* with reduced sensitivity to PZQ in Egypt and Senegal [59,60],  
  e.g. *S. mansoni* treatment failures in infected travellers [61],  
  e.g. *S. mansoni* phenotypic studies indicative of reduced PZQ susceptibility from Uganda [62],  
  e.g. *O. volvulus* with sub-optimal responses to IVM in Sudan Ghana [63,64],  
  e.g. *N. americanus* and *T. trichiura* with reduced sensitivities to both benzimidazoles [38,65]  
  Changes in genetic structure of parasite populations post MDA observed,  
  e.g. *S. mansoni* microsatellite population structure, in both treated and untreated individuals at the population level [66],  
  e.g. *O. volvulus*, particularly the β-tubulin gene [67] |
| High costs of resistance—limits spread and establishment of any evolved drug resistant genotypes,  
  e.g. *S. mansoni* in Egypt—same proportion of PZQ R after 10 years [59],  
  e.g. *S. mansoni* in laboratory—reduced fitness [47,48],  
  e.g. *O. volvulus* in the laboratory and field—lower female fertility [68] | Mathematical predictive models indicate, even with inherent costs of resistance, higher MDA selective pressures, as are now being dispensed within SSA, can allow resistant parasites to successfully invade and coexist between susceptible and resistant parasite strains [69,70] |
| Predicted large refugia for some NTDs e.g. schistosomes,  
  e.g. if MDA only in school-aged children [48,71],  
  e.g. if animal (including wildlife) host reservoirs [72],  
  e.g. if indirectly transmitted between human and intermediate host and vectors with differential selective pressures [73] | Predicted small refugia for some NTDs, e.g. for *W. bancrofti*  
  *S. mansoni* population genetic studies post PZQ indicate smaller refugia than predicted [66]  
  Current/recent MDA programmes are highly successful with high treatment coverage — strong selective pressures,  
  e.g. 100 million PZQ treatments in SSA for *S. mansoni* and *S. haematobium* by ScI; 250 million PZQ treatments per year for *S. mansoni* and *S. haematobium* through Merck KGaA donation |
| Population genetic substructure in some populations mitigates against evolution and/or establishment of resistance,  
  e.g. *S. mansoni* and *S. haematobium* [74,75] | Population genetic substructure in some populations favours the evolution and/or establishment of resistance,  
  e.g. *S. mansoni* and *S. haematobium* [74,75] |

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Table 1. (Continued.)

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<tr>
<td>Long generation mitigates against rapid evolution, e.g. average 7 years schistosomes</td>
<td>Parasite evolution over short time periods demonstrated when selective pressures sufficiently strong, e.g. S. mansoni in the laboratory [47]</td>
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<tr>
<td>Mixed species pairings and parthenogenic eggs mitigate against establishment of drug resistant strains, e.g. S. mansoni pairings with S. haematobium [48]</td>
<td>Mixed species pairings and introgressed viable hybrid progeny, e.g. S. haematobium pairings with S. bovis and/or S. currasoni [72], e.g. Ascaris lumbricoides pairings with A. suum [76]</td>
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trachoma and over one billion against STHs. The expansion of the treatment with PZQ also continues, and by 2016 there will be sufficient doses to treat at least 150 million people per year. Merck KGaA alone has promised to donate 250 million PZQ tablets per year by 2016, in addition to developing a new paediatric PZQ formulation. However, despite the expansion in schistosome MDA coverage with PZQ, from 12 million people in 2006 to 35 million people in 2011 and 100 million in 2013, schistosomiasis, like many of the NTDs, remains a major public health problem as transmission continues.

Current trajectories of bilateral support from US and UK governments will not be sufficient to ensure total coverage of people at risk from NTDs. In order to prioritize integrated MDA control, a number of suggestions have been made including the importance of emphasizing NTDs such as schistosomes and hookworm as major threats, either directly and/or as cofactors, to women’s and child health [10]. Hookworm-associated anaemia has been reported to occur in up to one-third of pregnancies in Africa [10]. Female genital schistosomiasis, caused by S. haematobium, may represent Africa’s most common gynaecological condition [10]. Female genital schistosomiasis has also been shown to increase a woman’s risk of acquiring HIV during intercourse and is a major cofactor in promoting virus transmission and hence contributing to Africa’s AIDS epidemic [10]. Despite such compelling evidence, none of the NTDs have, however, been prioritized by either the President’s Emergency Program for AIDS Relief (PEPFAR) or the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM).

Recently, a New York-based Ending Neglected Disease (END) Fund was established to raise private sector support for integrated NTD control (www.end.org). The END Fund operates in 16 countries, mostly in Africa, but also in India and Yemen, and has so far treated 30 million people. Other private non-governmental organizations, Deworm the World (DtW) and the Partnership for Child Development (PCD) are also mobilizing resources for NTD control, while a Global Network for NTDs (www.globalnetwork.org) based at the Sabin Vaccine Institute is providing programmes for NTD advocacy and awareness. Success in global NTD MDA will require substantial financial support beyond what is currently available from US, UK or private financial resources. The coming decade will require other donor country governments to step up and provide support, as well as the willingness of endemic countries to recognize that the unit costs are low and the donated drugs available, as well as beneficial and cost effective, and are all on the WHO Essential Medicines list. Certainly other North American and European countries will need to be involved, but recently a new analysis reveals a surprising burden of NTDs among the poor living in the group of 20 (G20) countries, including those that would benefit from integrated NTD control such as Argentina, Australia, Brazil, China, India, Indonesia, Mexico, Saudi Arabia and South Africa. Moving forward may require strategic diplomatic pressure from the USA and UK on these G20 nations to support NTD control in their own countries and among their neighbours [50].

4. Biological challenges to mass drug administration

As regards point (v), with such shifts in global health policy towards MDA implementation, intensive and prolonged new selective pressures will be placed on the infectious agents, which may have implications for the long-term success of these campaigns. An important lesson learned from the global attempts to eradicate malaria during the 1960s was the emergence of drug resistance from overreliance on a single medicine. In this sense, there is an enhanced risk for NTD drug resistance evolving because most of the NTDs are being targeted with only a single available drug used across hundreds of millions of people. Fortunately, there is limited evidence for established large-scale drug resistance for any of the NTDs to date. Unfortunately, there are very few programmes that specifically and systematically monitor for changes in drug efficacy or potential drug resistance, and many logistical and biological parameters in favour of its emergence (table 1).

For two STHs, Necator americanus and Trichuris trichiura, there are a number of reported instances for drug failure when albendazole or mebendazole are used in a single dose, and a recent meta-analysis indicated that both benzimidazoles anthelmintics can result in low cure rates [38,65]. Whether such apparent drug failures are due to bona fide resistance, as has been demonstrated for veterinary indications for this class of drug, or simply low coverage or some other mechanism, remains unclear. A recent multi-country study was performed in association with the WHO to monitor efficacy of benzimidazoles [77], the findings of which suggested that, based on faecal egg counts, a reduction of more than 95% for A. lumbricoides and more than 90% for hookworms should be the expected as minimum in all future surveys, and that therapeutic efficacy below this level following a single dose of albendazole should be viewed with concern of potential drug resistance. A standard threshold for efficacy against T. trichiura has yet to be established, as a single-dose of albendazole is unlikely to be satisfactory for this parasite, as it is in some areas for hookworm [78].
Table 2. Key challenges to control and ‘elimination’ for MDA-targeted NTDS (adapted from [39]).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biological</th>
<th>Socio-Geographic</th>
<th>Logistic</th>
<th>Strategic</th>
<th>Technical</th>
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<tbody>
<tr>
<td>Onchocerciasis</td>
<td>Very efficient vectors in Africa with high population numbers and long flight ranges</td>
<td>Cross border issues related to access to treatment for nomadic and refugee populations</td>
<td>Cost of monitoring and evaluation at low infection levels, including post elimination surveillance</td>
<td>Single annual treatment not adequate to achieve elimination in many parts of Africa</td>
<td>Gold Standard skin snip increasingly unacceptable and less sensitive</td>
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<td></td>
<td>Serious Adverse Events associated with IVM in <em>Loa loa</em> co-endemic areas</td>
<td>Hard to reach communities in post-conflict countries</td>
<td></td>
<td>Duration of current intervention ca 15 years</td>
<td>Limited laboratory capacity in endemic countries to perform novel diagnostic molecular and serological methods</td>
</tr>
<tr>
<td></td>
<td>Lack of macrofilaricides amenable to MDA strategy</td>
<td>Lack of incentives for community drug distributors</td>
<td></td>
<td>National government commitment</td>
<td>Lack of sensitive tools to detect exposure and early infection in humans</td>
</tr>
<tr>
<td></td>
<td>Potential for emergence of IVM-resistance</td>
<td>Persistent non-compliance</td>
<td></td>
<td></td>
<td>Not treating pregnant or lactating women, large swathes of population not treated for years</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>Persistence of infection in areas where the more efficient culicides are the main vectors</td>
<td>Persistent non-compliance makes effective coverage difficult</td>
<td>Cost of monitoring and evaluation at low infection levels, including post elimination surveillance</td>
<td>Long-term government commitment</td>
<td>ICT card test replaced by new test strip for antigen detection with more sensitivity; no need for cold chain, although test needs to be read after 10 min</td>
</tr>
<tr>
<td></td>
<td>Serious Adverse Events associated with IVM in <em>Loa loa</em> co-endemic areas</td>
<td>Effective coverage particularly challenging in small island populations and/or conflict and post-conflict countries</td>
<td></td>
<td>Resources for scaling up and maintaining national coverage</td>
<td>Antibody test to detect early infection currently under development and optimization</td>
</tr>
<tr>
<td></td>
<td>Lack of macrofilaricides amenable to MDA strategy</td>
<td></td>
<td></td>
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<tr>
<td>Schistosomiasis</td>
<td>Intermediate host present in water bodies with which populations have contact as part of their daily activities</td>
<td>Poor sanitation facilities prevent behavioural change to prevent faecal and urine contamination of water bodies</td>
<td>Distribution of up-scaled PZQ production demands better collaboration and funding</td>
<td>Implementation of complex strategy involving sectors other than health</td>
<td>Rapid diagnosis test to measure <em>S. haematobium</em> currently unavailable</td>
</tr>
<tr>
<td></td>
<td>Zoonotic infection (including hybridization) and transmission in Asia and potentially Africa</td>
<td>Poor sanitation facilities prevent behavioural change to prevent faecal and urine contamination of water bodies</td>
<td></td>
<td></td>
<td>Lack of sensitivity of Kato Katz test after treatment or in low intensity areas</td>
</tr>
<tr>
<td></td>
<td>Potential for emergence of PZQ-resistance—with no alternative drug available</td>
<td></td>
<td></td>
<td></td>
<td>Lack of suitable paediatric treatment</td>
</tr>
</tbody>
</table>

(Continued.)
As regards the filarial helminths, although not without controversy, studies in Ghana have identified that in some communities adult female *O. volvulus* worms were either non-responsive or resistant to the anti-fecundity effects of multiple treatments with IVM, with a rapid repopulation of the skin of microfilaria [63,64]. Changes in the genetic structure of these Ghanaian *O. volvulus* populations associated with IVM treatments were also observed, particularly on the β-tubulin gene, a gene associated with IVM resistance in the sheep intestinal nematode *Haemonchus contortus* [67]. These results illustrate how imperative MDA monitoring and evaluation (M&E) of drug efficacy is, although standardized IVM M&E remains lacking [64].

PZQ resistance in schistosomes remains equally controversial, but may be a particularly pertinent issue given that PZQ is the only available drug. While schistosomes have evolved resistance to oxamniquine in Africa [53–58], to date there is no indication regarding resistance of *S. japonicum* to PZQ in China despite its wide use [51]. However, a number of studies from the hospital, laboratory and field, combined with population genetic analyses demonstrating an impact of PZQ, all continue to raise concerns about the potential establishment of PZQ resistance [29,66,79]. On the positive side, there do appear to be high fitness costs associated with PZQ resistance [47,48,59,80]. However, mathematical models have suggested that, even with inherent costs of resistance, higher MDA selective pressures, as are now being dispensed within SSA, could allow resistant parasites to invade successfully and coexist between susceptible and resistant parasite strains [69,70]. As is the case for several of the NTDs, unfortunately PZQ efficacy has not been monitored on a systematic basis. However, a similar multi-country study to that undertaken for the STHs [77] has been recently initiated and the WHO have recently advised that 10% of all MDA implementation funds should be spent on M&E including drug efficacy [44]. Ideally, this should include both basic parasitological egg count measures and molecular analyses [74,75]. Whole-genome sequencing, in conjunction with powerful biostatistical techniques, has already begun to revolutionize many fields across the biosciences, including infectious disease epidemiology. Indeed, two recent major breakthroughs in understanding drug resistance in parasites, uncovering the locus responsible for artemisinin resistance in *Plasmodium falciparum* (PF3D7_1343700) [81], and oxamiquine resistance in *S. mansoni* (Smp_089320) [58] would not have been possible without whole genome sequencing, and these should soon be available for all the major NTDs to help understand their biology and ultimate control [82].

Drug resistance is not the only explanation for apparent treatment failures. One may simply be low MDA coverage and compliance issues, another is natural tolerance and/or rapid transmission, including the potential role of additional animal reservoirs. Many NTDs are also diseases of substantial veterinary importance. Moreover, many of these are zoonotic—i.e. diseases that can be transmitted, directly or indirectly, from animals to humans. While there are no, as yet, known animal reservoirs for *O. volvulus* or *W. bancrofti*, *B. malayi* is found in cats and leaf monkeys (*Presbytis*) [83], and may be responsible for recent re-emergence cases of *B. malayi* in Sri Lanka after 20 years of successful MDA. Cross-infections have been demonstrated between *Ascaris* of humans and pigs in sympatric areas [76], and dogs and cats, for example, are known successful reservoirs for some of the food-borne trematodes such as *Opisthorchis viverrini*...
in Thailand [84]. Schistosoma japonicum remains endemic in China despite five decades of multi-faceted interventions, including MDA, mollusciciding, health education, sanitation and environmental improvement [85], and has re-emerged in some areas where it was thought to have been eliminated [86]. Spill-over from animal reservoirs appears to be maintaining such human schistosomiasis through a combination of bovine livestock and, as recently identified, rodent wildlife, depending on the habitat type [87–93]. The finding that rodents can act as a major S. japonicum infection reservoir poses particular challenges for MDA given the notorious logistical difficulties in achieving rodent control itself [87,90]. Similar challenges are presented in the Philippines, where parasitological and molecular analyses have revealed dogs to be partially responsible for maintaining transmission and subsequent human infections despite human MDA [94]. The potential for ongoing transmission through zoonotic reservoirs is not the reserve only of the Asian NTDs, as modern molecular diagnostic techniques are beginning to reveal. Non-human primates, rodents and insectivores are responsible for human S. mansoni infections in some regions of Africa and the Caribbean [95–97]. While S. haematobium was believed to be essentially an exclusively human-specific parasite [98], recent molecular studies have confirmed bidirectional hybridization between S. haematobium with the animal (cattle, goat and sheep) schistosome species S. bovis [99] and S. carassoni among infected children in West Africa [72]. The implications of zoonotic hybrids on transmission potential are substantial, particularly in terms of the potential for increased definitive and intermediate host ranges, hybrid vigour, as well as differential PZQ susceptibilities. Another NTD targeted for eradication, albeit through sanitation, intermediate host control, health education and behavioural change rather than MDA, is that of the Guinea worm (dracunculiasis) through the Guinea Worm Eradication Program (GWEP). Dracunculiasis was rediscovered in Chad in 2010 after an apparent absence of 10 years, and perhaps most notable of all, dogs were found to be infected. Molecular sequencing indicated that both human and dog infections were caused by the same Dracunculus medinensis, and thus it appears that dogs may now be serving to sustain transmission in Chad [100]. The questions must therefore now be asked regarding how MDA and M&E programmes should be modified to accommodate potential host-switching and/or zoonotic transmission. Whilst animal reservoirs provide challenges to successful MDA, at the same time they may provide benefits in terms of increased refugia mitigating against the establishment and spread of drug resistance [48]. Understanding the complex population biology of multi-host pathogens has been declared as one of the major challenges of biomedical sciences for the twenty-first century [101–103]. This highlights the theoretical, as well as the clinical and public health relevance of research into the population biology and disease transmission dynamics of multi-host–parasite systems if we are ever to achieve control or potential elimination.

5. Conclusion and the way forward
We are living in an exciting time where MDA of certain NTDs has already had a huge impact on preventing or relieving morbidity and ultimately in improving global health, particularly among the poorest of the poor. The coming decade could witness substantial declines in the prevalence, intensity and public health importance of at least nine targeted NTDs, i.e. the three STH infections, schistosomiasis, LF, onchocerciasis and trachoma [2,4,7], in addition to yaws and scabies [14]. For global elimination and other ambitious targets set by the 2012 London Declaration on NTDs and the 2013 WHA resolution on NTDs, there are, however, many challenges that must be surmounted (table 2). As only 37% of the world’s impoverished people who require MDA actually receive any essential NTD drugs [45], at least one billion people who need these medicines are not receiving them. We need to promote the leadership of the US and UK governments for the outstanding examples they have set for the world in financing NTD programmes and advocating for their consideration as a higher priority in global health. The emerging economies of the G20 must now also be encouraged to commit to NTD global control and elimination efforts, including within conflict and post-conflict countries [50]. Potentially, LF, trachoma, yaws and scabies could be eliminated globally, and onchocerciasis could be eliminated in the Americas and several SSA countries. Although it is doubtful that these diseases would be eliminated on a global scale, the impact of expanded MDA on STH infections, schistosomiasis and onchocerciasis will be substantial. If NTDs are prioritized they could become a true success story in the post-2015 MDG agenda. However, MDA alone is unlikely to be sufficient in the long term. New or additional drugs or vaccines are required [37,50], together with a greater backing for research into the basic biology, evolutionary potential and transmission dynamics of these diseases. There must be an emphasis on improving the efficiency of the MDA strategy, by developing improved M&E tools, including that relating to any loss of drug efficacy or emerging resistance. Approaches to ensuring sustained high coverage over repeated years will need health education programmes to fit local social and cultural settings. We must strive to deliver MDA to all the inhabitants of endemic communities, but also to improve living conditions and in particular access to education, water and sanitation. Until, and unless, these are achieved, ongoing MDA will be necessary to control morbidity, ideally reducing NTDs to the status of ‘not a public health problem’, but the breaking of transmission will not be achieved, at least within the target date.

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References


