**Title**

More medicines alone cannot ensure the treatment of neglected tropical diseases

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**Abstract**

Neglected tropical diseases afflict more than one billion of the world’s poorest people. Annual pharmaceutical donations of billions of preventive chemotherapies for neglected tropical diseases enable the largest en masse treatment campaigns globally with respect to the number of people targeted for treatment. However, the blanket distribution of medicines at no cost to individuals in need of treatment does not guarantee that those individuals are treated. Here we argue that the expansion of medicine donations programmes and the development of new medicines are not the primary solutions to sustaining and expanding the growth of neglected tropical disease programmes. Treatment often is not verified; access to medicines may not be equitable across at-risk populations; and treatment targets for disease control remain largely unmet within many endemic countries. For the more equitable access to and efficient use of existing medicines, research is needed now on how best to integrate the treatment of neglected tropical diseases into local health systems. A comprehensive approach should be employed that combines mass drug administration with on-demand access to treatment. Increased endemic country commitment to and ownership of treatment campaigns is essential to improve the access to medicines for neglected tropical diseases.

**Mass drug administration: reconceptualising treatment from clinics to campaigns**

Individual affliction with a neglected tropical disease (NTD) predominantly is a direct indicator of extreme poverty, signaling financial deprivation, social marginalization, and vulnerability.1,2 Though infrequent, NTDs also are observed in non-endemic areas in immigrants and travellers.3 The most prevalent and morbidity-inducing NTDs include schistosomiasis, lymphatic filariasis, onchocerciasis, trachoma, and soil-transmitted helminths; these chronic infections affect at least one billion individuals with many more individuals at risk of infection (Table 1).4 An estimated 6·35 million disability adjusted life years (DALYs) were caused by these NTDs in 2017.5 For example, if left untreated, intestinal schistosomiasis can cause hepatosplenomegaly, liver fibrosis, portal hypertension, anaemia, and diarrhoea.6 The populations at risk of NTDs have limited access to safe sanitation, potable water, or government health centres, and in many cases such destitution is further exacerbated by conflict.7,8 Within these endemic poor communities, individuals with the greatest morbidity attributable to NTDs are of the lowest socioeconomic status, stigmatized, and on the periphery of village social networks.7,9-13

The concept and scale of treatment for NTDs is unique. To accommodate the number of at-risk individuals and resource constraints within endemic countries, public health approaches for chronic parasitic infections were reconceptualised. Treatment approaches for these non-vaccine treatable pathogens with high reinfection rates were changed from diagnose-and-treat strategies within clinics to diagnosis-free medicine distribution campaigns within at-risk communities. Vastly different diseases1, which vary by pathogen, vector/intermediate host, transmission dynamics, life cycle, morbidity caused, and medicines used, are targeted with a single vertical treatment approach—mass drug administration (MDA). MDA is the mainstay of treatment for schistosomiasis, lymphatic filariasis, onchocerciasis, trachoma, and soil-transmitted helminths.14 These diseases are commonly referred to as preventive chemotherapy NTDs (PC-NTDs) because they are amenable to MDA using preventive chemotherapies (PCs). The aim of MDA is to deliver oral, single-dose PCs to all at-risk individuals irrespective of infection status. Volunteer lay health workers, village members, and schoolteachers are trained to administer treatments. MDA is a vertical approach in that donated PCs are not available to local health centres. These blanket treatment programmes have shown remarkable success in making available treatment for diseases that are otherwise of low priority in national health systems1. There are several possible reasons why PC-NTDs are of low priority within health systems of endemic countries. 1) PC-NTDs cause morbidities attributable to many diseases that manifest over long time periods.15 The chronic differentiated nature of PC-NTDs may result in both policymakers and patients discounting the clinical consequences of PC-NTDs, most detrimentally by underestimating/dismissing potential DALYs and deaths. 2) PC-NTDs predominantly affect the poorest individuals who may have few political freedoms and insufficient access to government health care to report on the need for treatment.1 3) The massive scale of pharmaceutical medicine donations and international aid for MDA might crowd out within-country incentives to invest in PC-NTDs.

Over one billion people were reported to receive treatment through MDA in 2017 (Table 1).16 The largest medicine donation programmes worldwide were established to enable MDA.17 Pharmaceutical companies, including but not limited to Eisai, Johnson & Johnson, GlaxoSmithKline, Merck KGaA, Merck Sharp and Dohme, and Pfizer manufacture and donate billions of tablets, capsules, and liquid form PCs at no cost to the World Health Organization (WHO).18 Endemic countries apply to the WHO19 or work with non-profit organizations to procure dosage forms for a diversity of treatments delivered during MDA. Coupled with implementation support from non-profit organizations (e.g. the Bill and Melinda Gates Foundation, END Fund, Children’s Investment Fund Foundation, and Kuwait Fund) and high-income country governments (predominantly the United Kingdom and United States), the value of these philanthropic contributions is unprecedented. In April 2017, the Guinness Book of World Records confirmed that this was the largest public health donation ever made20 and to celebrate five years of MDA achievements since the donations were consolidated by the London Declaration17, pharmaceutical companies and donors pledged an additional ~£613 million ($812 million) for medicine donations and implementation support.21 These pledges were led by the U.K. Department for International Development, which committed £360 million (>$476 million) over five years in MDA implementation support.22 All received and pledged medicine donations for NTDs and MDA have been valued at ~£13 billion ($17 billion)21, although it is not transparent how medicine costs were estimated.

**Two-thirds of the way: translating massive medicine donations into equitable treatment**

MDA is at the heart of the WHO’s access strategy for PC-NTDs.14 Donated medicines and blanket treatment campaigns have proven crucial for increasing advocacy, establishing initial treatment regimens, and substantially controlling or progressing towards eliminating the most prevalent NTDs. However, these steps are insufficient to ensure equitable access to treatment. In Figure 1, we propose a conceptual framework for the sustainable treatment of NTDs. Medicine donations and ‘rapid-impact’ treatment strategies constitute essential early steps towards delivering medicines in a sustainable manner to at-risk individuals. These early steps brought MDA 70% (3·5/5 steps) of the way along the critical path to equitable treatment access. In the 1970s, substantial progress for disease prioritization (step 1), treatment design (step 2), and market availability (step 3) for NTDs was observed. First generation en masse treatment programmes were formed.23 24,25 The Onchocerciasis Control Programme (OCP) was set up in 1974. In 1995, treatment for onchocerciasis rapidly expanded within West Africa due to ‘unlimited’ donations of ivermectin by Merck Sharp and Dohme for the establishment of the African Programme for Onchocerciasis Control (APOC).26 The reach of MDA accelerated under APOC, serving as a paradigm for additional PC-NTD programmes. In the early 2000s, increased advocacy for schistosomiasis, lymphatic filariasis, trachoma, and STHs enabled further expansion of MDA.14,23,27,28 This advocacy26 garnered critical resources to provide treatment for multiple NTDs in endemic countries (½ of step 4) and improved the market availability of medicines (step 3, Figure 1).18

Currently, the major focus for equitable access to treatment remains on market availability (step 3).29 Increased medicine donations are prioritized and medicine development is incentivized.17,30 Here we examine the last steps (steps 4-5, Figure 1) to equitable treatment access, i.e. health system integration and the role of endemic countries in ensuring medicines are delivered. We argue that a new approach, which is data-driven and focused on increased verification and accountability of local governments is needed for MDA.

**How do we know if someone was treated?**

The blanket treatment strategy of MDA does not require knowledge of individual infection status; however, there remains a need to verify if an individual received and complied with treatment. WHO guidelines for morbidity control or elimination depend on the percentage of the target population treated.31 In a clinical setting, a nurse or doctor, in theory, administers and observes treatment. In a MDA campaign, national programmes rely on a chain of individuals to report where medicines were distributed.32 The information reported takes one of two forms: medicine distribution inventories or during/post-MDA surveys.33 The former traces the number of medicines delivered to an administrative unit, whereas the latter uses accounts from the lay medicine distributors (most common) or independent surveyors who collect information on treatment delivery directly from recipients at primary schools or within communities. Both methods exhibit problems of over reporting of treatments administered, incomplete data, inaccurately aggregated data, and little information on individual treatment rates when compared to aggregated treatment rates.7,33-35 Observations from independent surveyors are used as the benchmark of true population treatment rates. These post-MDA validation surveys will be inaccurate when sentinel sites or sampling groups are not representative of the whole target population and patient recall is low.

Concerning patient compliance, directly observed therapy (DOT)36 is recommended for MDA. With DOT for MDA, patients ingest medicines in the presence of lay medicine distributors. Information is needed concerning how many countries provide DOT training to lay medicine distributors during annual MDA activities. For countries that provide DOT training for MDA, DOT in practice is not verified. Any methods to verify DOT would require providing disaggregated data by patient or medicine distributor. One potential method of verifying DOT might be to establish report cards for patients to self-report/monitor compliance. For tuberculosis, this method has been shown to be just as effective in increasing compliance with treatment when compared to a strict form of DOT where patients were observed in a clinical setting.36

Treatment verification is challenging when medicine delivery indicators are poorly defined for MDA. WHO guidelines for treatment coverage focus on medicine ingestion.32 Yet, medicine delivery cannot be equated with medicine ingestion.9 Factors that predict whether an at-risk individual is likely to be offered medicines (delivery) differ from the determinants of medicine ingestion.7,9,10 A focus on ingestion leads to the downstream blaming of recipients of MDA, which in turn results in intensified health education campaigns to convince individuals to participate in MDA.37 However, the recognition of MDA as a two-step process—first medicine delivery (supply) then ingestion (demand)—can help reveal detailed issues (step 5, Figure 1) that explain differences in reported and validated treatment coverage. For example, inappropriately timed MDA implementation or social biases of medicine distributors may cause marginalised individuals to be systematically missed, thus not providing them the option to decide to participate in MDA.7,38 The NTD community must use standard terminology to distinguish delivery from the ingestion of medicines.34 This distinction is needed for endemic countries to distinguish between contexts that require alternative modes of medicine delivery or intensified health education.39

The detailed data required to verify treatment and distinguish medicine delivery from ingestion pose challenges to local health systems. Capacity is needed to analyze individual-level data in nearly real time, to respond to unusual patterns or inaccuracies in reporting, and to frequently conduct visits to monitor endemic communities. Presently, the WHO PC (PCT) Database40 contains government-reported treatment rates at the national level. This reported information is sparse, does not necessarily accord with post-MDA validated surveys, and provides no information on the verification measures (if any) used for data retrieved from endemic areas.41 Progress is being made by the Expanded Special Project for Elimination of NTDs (ESPEN) in sub-Saharan Africa to provide technical support for a more complete, subnational tracking of MDA.42 With ESPEN, local NTD officers will be better placed to train workers within local health systems.

**Donated medicines ≠ access to treatment for everyone**

Medicine donation programmes, despite their scale, do not address all steps needed for equitable access to treatment for NTDs (Figure 1).16 One reason is that medicine donations are not necessarily based on infection epidemiology and therefore, do not reach all individuals in need of treatment. Albendazole is not donated to treat adults with hookworm infections, though these individuals have been shown to have the heaviest infection intensities thereby acting as parasite reservoirs and predisposing school-aged children who receive donated medicines to infection.11,43,44 For middle to high-income countries, there are no medicine donations for PC-NTDs.45 There is an assumption that individuals, for whom medicines are not donated, will receive treatment through existing health systems. Yet, as previously noted, PCs are not available from hospitals or health centres. To revise medicine donation regimens or to establish procurement models beyond donations, new treatment guidelines for all individuals currently at high risk of PC-NTDs are required from the WHO.46

In countries with sufficient medicine donations to treat nearly all at-risk individuals, the current vision of access47 has unrealized levels of treatment coverage (medicine delivery). In 2017, many countries failed to meet WHO treatment targets (65-75% of at-risk individuals) across all PC-NTDs.16 This failure is indicative of poor medicine delivery.41 For example, in Mayuge District, Uganda, individuals most heavily infected with schistosomes or hookworm are less likely to be offered medicines despite provision of a sufficient number of PCs to lay medicine distributors.7,9,10 There also are wastages of medicines by national MDA programmes. Imprecise mapping of infection prevalence results in overestimations of the number of individuals requiring treatment.48 Suboptimal medicine delivery and wastages may undermine pharmaceutical company commitments to increase or continue donations.49 If donations are reduced or temporarily stopped then MDA will be disrupted in endemic areas, thereby halting the access to PCs for at-risk individuals. Consequently, without access to treatment within local health centres, a relapse to baseline prevalence or intensity, in particular for schistosomiasis or soil-transmitted helminths, will ensue.50

For more equitable access to and efficient use of existing medicines, recommendations are needed from the WHO to integrate treatment for NTDs into Universal Health Care (UHC) delivery packages (expansion of step 2, Figure 1). UHC is a priority objective of the WHO.51 In 2017, the WHO along with the World Bank and other international organizations affirmed that country-led UHC is technically and financially feasible. Yet, there is little guidance for implementation research from the WHO that would facilitate the integration of PC-NTDs into local health systems. Instead, there is emphasis on the benefits of existing vertical MDA in either addressing the goals of UHC or serving as a proxy indicator for progress towards UHC.47,52

**Increased medicine options ≠ increased treatment rates**

A greater diversity of treatment options for PC-NTDs does not necessarily lead to improved access to treatment. The WHO approval of PCs, i.e. the inclusion of PCs on the WHO Model List of Essential Medicines,53 neither represents the variety/number of medicines individuals can access nor the affordability of WHO-approved medicines.54 New combinations of existing PCs are being used within MDA to establish more effective treatment regimens for lymphatic filariasis. Triple medicine therapy—ivermectin plus diethylcarbamazine plus albendazole (IDA)—better reduces microfilarial loads when compared to the standard two-medicine regimen of diethylcarbamazine plus albendazole.55,56 Both regimens are comparable in their reductions of macrofilarial loads. To provide benefits beyond the standard regimen, IDA relies on achieving currently unrealized high rates of treatment delivery and compliance.57 16 The new regimen also nearly doubles the number of pills/tablets provided to patients per single-dose treatment. Concerning new medicines, incentive schemes for the pharmaceutical industry to invest in tropical medicine such as the United States’ Priority Review Vouchers have no requirement that these new medicines are delivered to at-risk or infected individuals.30,58,59 NTD not-for-profit consortiums60-62 are in place to develop new medicines for onchocerciasis, lymphatic filariasis, and schistosomiasis. Yet, at least for the treatment of schistosomiasis in preschool-aged children, there is no commitment to donate the new medicines.63,64 An access strategy for PC-NTDs that moves away from donated medicines and blanket treatment requires a better understanding of data-driven, computational approaches to guide treatments to the right individuals in the right place at the right time.65,66 Notably, the evaluation of the need for new medicines is difficult in areas with poor medicine delivery rates. In such areas, there is the challenge of untangling problems of high pathogen transmission, pharmacological resistance, and limited medicine efficacy from behavioural issues limiting the access to PCs for at-risk individuals. The former warrant the development of better diagnostics and new medicines, whereas the latter require revised government implementation, monitoring, and accountability strategies. Confounding these issues diverts essential funding and research away from helping the individuals afflicted with NTDs. Only precise tracking and verification of treatment will be able to identify which issue should be pursued.

**Way forward – A more comprehensive view of treatment for PC-NTDs**

The exceptional scale of medicine donations from the pharmaceutical industry has led to unprecedented levels of MDA for PC-NTDs that has improved disease control for over one billion people.1,67 However, the continued expansion of medicine donation programmes is not the only method of increasing/sustaining the treatment of PC-NTDs. The quantity of PC donations now exceeds the capacity of endemic countries to deliver PCs.68 Instead, embracing a more comprehensive view of treatment (Figure 1) will result in the more efficient use of existing medicines. There is a need to 1) better target at-risk populations, 2) improve treatment verification, and 3) overturn the view that treatment is synonymous with the availability of PCs.

For MDA, test-and-treat strategies, which require improved rapid diagnostics, may reduce implementation costs in low transmission areas or increase treatment rates of noncompliant populations. More detailed spatial mapping based on disease ecology, especially for focal diseases such as schistosomiasis,48 may improve prevalence mapping not only for MDA, but also for selecting local health centres to administer PCs. In addition to more efficiently directing PCs to individuals in need of treatment, more accurate maps may reduce the quantity of donated PCs required. These methods to improve the targeting of at-risk populations also may increase patient safety in communities where *Loa loa* is endemic and PC (ivermectin) cannot be administered en masse.69

To directly confirm that a patient was present during treatment, existing tools such as DOT and sentinel site surveys should be combined with emerging technologies. Examples include mobile phone reports for either tracking supply chains in real time or receiving confirmations directly from patients, and biometric tools for iris scanning and digital fingerprinting.70,71 These emerging verification methods may increase the accountability of MDA programmes by reducing data misrepresentation, errors, and incompleteness whilst also making data immediately available for analysis in local health systems. Disease control also can depend on vector control and water, sanitation, and hygiene.72,73 Without these complementary interventions, MDA may be undermined by high reinfection rates and, in turn, unnecessarily prolonged.

A comprehensive approach is needed now that combines MDA with on-demand access to treatment within local health systems, where appropriate, as well as enhanced accountability and country ownership. Future research should examine country experiences to understand how massive medicine donation programmes affect the way that national health systems respond to PC-NTDs. This work would provide insight into the barriers, if any, of integrating the treatment of PC-NTDs into UHC delivery packages. With WHO 2020 goals74 fast approaching and pharmaceutical commitments heavily aligned with these goals, medicine donation programmes may be curtailed in the near future. Alternative strategies for sustaining the growth of NTD programmes are needed that do not rely on more medicines.

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GC and DB declare no competing interests. Funders had no role in this analysis, writing of this manuscript, or decision to submit for publication.

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**TABLES**

**Table 1** Estimated prevalence and number of treatments (in millions) for PC-NTDs in 2017

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Disease** | **No. of individuals infected4** | **DALYs5** | **No. of countries requiring PCs** a **16** | **No. of people requiring PCs16** | **Reported no. of individuals receiving PCs16** |
| Schistosomiasis | 142·79 | 1·43 | 52 | 212·70 | 96·70 |
| Lymphatic filariasis | 64·62 | 1·36 | 52 | 888·90 | 465·10 |
| Onchocerciasis | 20·94 | 1·34 | 31 | 205·20 | 136·50 |
| Trachoma | 3·82 | 0·30 | 40 | 165·10 | 83·50 |
| Soil-transmitted helminths | 894·92 | 1·92 | 101 | 856·10 | 489·20 |

a114 countries in total

**FIGURE LEGENDS**

**Figure 1. A comprehensive approach for the sustainable treatment of NTDs.** This figure presents a conceptual framework for understanding the progression towards the equitable access to treatment for NTDs and the integration of NTDs into local health systems. The text in dash-lined boxes represents priority areas requiring additional research to support the growth of NTD programmes and facilitate the inclusion of the treatment of NTDs in Universal Health Care (UHC) delivery packages. The steps shown are not mutually exclusive. Feedback loops and co-dependencies between the different steps exist. DNDi = drugs for neglected diseases initiative. PZQ = praziquantel. A·WOL = anti-wolbachia. PCs = preventive chemotherapies.