More medicines alone cannot ensure the treatment of neglected tropical diseases

Gaylette F Chami, Donald A P Bundy

Neglected tropical diseases afflict more than 1 billion of the world’s poorest people. Pharmaceutical donations of preventive chemotherapy 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. In this Personal View, we aim to examine the next steps that need to be taken towards ensuring equitable treatment access, including health system integration and the role of endemic countries in ensuring medicines are delivered to patients. We argue that the expansion of medicine donation programmes and the development of new medicines are not the primary solutions to sustaining and expanding the growth of neglected tropical disease programmes. Treatment is often not verified by a medical professional, independent surveyor, or national programme officer. Additionally, access to medicines might not be equitable across at-risk populations, and treatment targets for disease control remain largely unmet within many endemic countries. To enable equitable access 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 used, which combines mass drug administration with on-demand access to medicines. Treatment is often not preventive chemotherapy for neglected tropical diseases enable the largest en masse treatment campaigns globally. Preventive chemotherapy (PC) for NTDs because they are amenable to MDA using PC. These blanket treatment programmes have shown remarkable success in making available treatment for diseases that are otherwise of low priority in national health systems.

Mass drug administration: reconceptualising treatment from clinics to campaigns

Affliction with a neglected tropical disease (NTD) is generally a direct indicator of extreme poverty, signalling financial deprivation and social marginalisation. Though infrequent, NTDs are also observed in non-endemic areas in immigrants and travellers. The most prevalent NTDs, causing greatest morbidity and mortality, include schistosomiasis, lymphatic filariasis, onchocerciasis, trachoma, and soil-transmitted helminths; these chronic infections affect at least 1 billion individuals with many more individuals at risk of infection (table). An estimated 6·35 million disability adjusted life-years (DALYs) were caused by these NTDs in 2017. For example, if left untreated, intestinal schistosomiasis can cause hepatosplenomegaly, liver fibrosis, portal hypertension, anaemia, and diarrhoea. The populations at risk of NTDs have inadequate access to safe sanitation, potable water, or government health centres, and in many cases such destitution is further exacerbated by conflict. Within these endemic poor communities, individuals with the greatest morbidity attributable to NTDs are of the lowest socio-economic status, stigmatised, and on the periphery of social networks.

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 in the 1970s. 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 diseases, which vary by pathogen, vector or intermediate host, transmission dynamics, lifecycle, 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. These diseases are commonly referred to as preventive chemotherapy (PC)-NTDs because they are amenable to MDA using PC. The aim of MDA is to deliver oral, single-dose PC 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 drugs are not available to local health centres, but instead are administered through scheduled campaigns. These blanket treatment programmes have shown remarkable success in making available treatment for diseases that are otherwise of low priority in national health systems.

Several possible reasons have been proposed as to why PC-NTDs are of low priority within health systems of endemic countries. First, PC-NTDs cause morbidities

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of individuals infected (in millions)</th>
<th>Disability adjusted life-years (in millions)</th>
<th>Number of countries requiring PC</th>
<th>Number of people requiring PC (in millions)</th>
<th>Reported number of individuals receiving PC (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis</td>
<td>142.79</td>
<td>1.43</td>
<td>52</td>
<td>212.70</td>
<td>96.70</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>64.62</td>
<td>1.36</td>
<td>52</td>
<td>888.90</td>
<td>465.10</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>20.94</td>
<td>1.34</td>
<td>31</td>
<td>205.20</td>
<td>136.50</td>
</tr>
<tr>
<td>Trachoma</td>
<td>3.82</td>
<td>0.30</td>
<td>40</td>
<td>165.10</td>
<td>83.50</td>
</tr>
<tr>
<td>Soil-transmitted helminths</td>
<td>894.92</td>
<td>1.92</td>
<td>101</td>
<td>856.10</td>
<td>489.20</td>
</tr>
</tbody>
</table>

Table: Estimated prevalence and number of treatments (in millions) for neglected tropical diseases in 2017

Personal View

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attributable to many diseases that manifest over long time periods. The chronic differentiated nature of PC-NTDs might result in both policy makers and patients discounting the clinical consequences of PC-NTDs, most detrimentally by underestimating or dismissing potential DALYs and deaths. Second, PC-NTDs predominantly affect the poorest individuals who might have few political freedoms and insufficient access to government health care to report on the need for treatment. Third, the massive scale of pharmaceutical medicine donations and international aid for MDA might reduce within-country incentives to invest in NTDs amenable to PC.

More than 1 billion people were reported to receive treatment through MDA in 2017 (table). The largest medicine donation programmes worldwide were established to enable MDA. Pharmaceutical companies, including but not limited to Eisai, Johnson & Johnson, GlaxoSmithKline, Merck KGaA, Merck Sharp & Dohme, and Pfizer manufacture and donate billions of tablets, capsules, and liquid form PC at no cost to WHO. Endemic countries apply to WHO or work with non-profit organisations to procure dose forms for a diversity of treatments delivered during MDA. Coupled with implementation support from non-profit organisations (eg, Bill & Melinda Gates Foundation, The END Fund, Children’s Investment Fund Foundation, and the Kuwait Fund) and high-income country governments (predominantly the UK and USA), the value of these philanthropic contributions is unprecedented. In April, 2017, the Guinness Book of World Records confirmed that this donation was the largest public health donation ever made and to celebrate 5 years of MDA achievements since the donations were consolidated by the London Declaration, pharmaceutical companies and donors additionally pledged around £613 million (US$812 million) for medicine donations and implementation support. These pledges were led by the UK Department for International Development, which committed £360 million (>US$476 million) over 5 years in MDA implementation support. All received and pledged medicine donations for NTDs and MDA have been valued at around £13 billion ($17 billion), although it is not transparent how medicine costs were estimated.

Two-thirds of the way: translating large-scale medicine donations into equitable treatment

MDA is at the heart of the WHO’s access strategy for PC-NTDs. 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 the figure, we propose a conceptual framework, which is split into five steps, for the sustainable treatment of NTDs. Medicine donations and rapid-impact treatment strategies constitute essential early steps towards delivering medicines in a sustainable early steps at-risk individuals. These early steps brought MDA 70% (3-5 of five steps) of the way along the crucial path to equitable treatment access. In the 1970s, substantial progress for disease prioritisation (step 1), treatment design (step 2), and market availability (step 3) for NTDs was observed. First generation chemotherapy treatment programmes were formed. The Onchocerciasis Control Programme was set up in 1974. In 1995, treatment for onchocerciasis rapidly expanded within west Africa due to unlimited donations of ivermectin by Merck Sharp & Dohme for the establishment of the African Programme for Onchocerciasis Control. The reach of MDA quickly increased under this programme, serving as a paradigm for additional PC-NTD programmes. In the early 2000s, increased advocacy for schistosomiasis, lymphatic filariasis, trachoma, and soil-transmitted helminths enabled further expansion of MDA in the US and WHO. In 2017, the Guinness Book of World Records confirmed that this donation was the largest public health donation ever made and to celebrate 5 years of MDA achievements since the donations were consolidated by the London Declaration, pharmaceutical companies and donors additionally pledged around £613 million (US$812 million) for medicine donations and implementation support. These pledges were led by the UK Department for International Development, which committed £360 million (>$476 million) over 5 years in MDA implementation support. All received and pledged medicine donations for NTDs and MDA have been valued at around £13 billion ($17 billion), although it is not transparent how medicine costs were estimated.

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. 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. The information reported takes one of two forms: medicine distribution inventories or during or post-MDA surveys. Medicine distribution inventories trace the number of medicines delivered to an administrative unit, whereas surveys use accounts from the lay medicine distributors (most common) or independent surveys 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 with aggregated treatment rates.
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) 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 or monitor compliance. For tuberculosis, this method has been shown to be just as effective in increasing compliance with treatment when compared with a strict form of DOT in which patients were observed in a clinical setting.

Treatment verification is challenging when medicine delivery indicators are poorly defined for MDA. WHO guidelines for treatment coverage focus on medicine ingestion. Yet, medicine delivery cannot be equated with medicine ingestion. Factors that predict whether an at-risk individual is likely to be offered medicines (delivery) differ from the determinants of medicine ingestion. 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. 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) that explain differences in reported and validated treatment coverage. Inappropriately timed MDA implementation or social biases of medicine distributors might cause marginalised individuals to be systematically missed, thus not providing them the option to decide to participate in MDA. The NTD community should use standard terminology to distinguish delivery from the ingestion of medicines. This distinction is needed for endemic countries to distinguish between contexts that require alternative modes of medicine delivery or intensified health education.

The detailed data required to verify treatment and distinguish medicine delivery from ingestion pose challenges to local health systems. Capacity is needed to perform the detailed data required to verify treatment and distinguish medicine delivery from ingestion.

Figure: A comprehensive approach for the sustainable treatment of NTDs

A conceptual framework is proposed for understanding progression towards equitable access to treatment for NTDs and the integration of NTDs into local health systems. Dash-lined boxes represent priority areas requiring additional research to support the growth of NTD programmes and facilitate the inclusion of the treatment of NTDs in universal health coverage delivery packages. The steps shown are not mutually exclusive. Feedback loops and co-dependencies between the different steps exist. NTDs=neglected tropical diseases. DNDi=Drugs for Neglected Diseases initiative. PC=preventive chemotherapy.

Steps | Key considerations | Actors, determinant, or outputs
--- | --- | ---
1 | Disease prioritisation | Pathogen identification, Patient diagnosis, Knowledge of morbidity and key populations at risk | External, Increased proportion of global health funding, Internal, Increased ranking relative to all endemic diseases |
2 | Treatment options | Pre-clinical research, Clinical trials, Market dossiers | New medicines, Repurposed medicines |
3 | Market availability | WHO | Production capacity, Essential medicines list, Production capacity |
4 | Endemic country treatment delivery | Vertical, Mass drug administration | Disease specific, Scheduled campaigns, Blanket treatment, No diagnosis, Unpaid health workers, No PC for purchase, No PC in health centres |
5 | Equitable treatment of at-risk individuals | Supply, medicine delivery, Community demand, System demand, Health system demand | Data collection, Monitoring, Appropriate indicators, Verification, Local incentives or motivations, Implementation strategy |

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analyse individual-level data in nearly real-time, to respond to unusual patterns or inaccuracies in reporting, and to frequently visit endemic communities for monitoring. At present, the WHO PCT databank 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. Progress is being made by the Expanded Special Project for Elimination of NTDs in sub-Saharan Africa to provide technical support for a more complete, subnational tracking of MDA. With the project, local NTD officers will be better placed to train workers within local health systems.

**Donated medicines do not equal 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). 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, although these individuals have been shown to have the heaviest infection intensities thereby acting as parasite reservoirs and predisposing children typically aged 5–14 years who receive donated medicines to infection. For middle-income to high-income countries, there are no medicine donations for PC-NTDs. 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 WHO.

In 2017, many countries did not meet WHO treatment targets for MDA, which are set at 65–75% of at-risk individuals across all PC-NTDs. This figure is indicative of poor medicine delivery. 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. Medicines are also wasted by national MDA programmes. Imprecise mapping of infection prevalence results in overestimations of the number of individuals requiring treatment. Suboptimal medicine delivery and wastages could undermine pharmaceutical company commitments to increase or continue donations. 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 helminthes, will ensue.

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

**Increased medicine options do not equal increased treatment rates**

A greater diversity of treatment options for PC-NTDs does not necessarily lead to improved access to treatment. WHO’s approval of PCs (ie, the inclusion of PCs on the WHO Model List of Essential Medicines) neither represents the variety or the number of medicines individuals can access nor the affordability of WHO-approved medicines. 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 albenzazole (IDA)—better reduces microfilarial loads when compared with the standard two-medicine regimen of diethylcarbamazine plus albenzazole. Both regimens are similar in their reductions of macrofilarial loads. To provide benefits beyond the standard regimen, the triple medicine therapy relies on achieving currently unrealised high rates of treatment delivery and compliance. The new regimen also nearly doubles the number of pills or 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. NTD not-for-profit consortiums are in place to develop new medicines for onchocerciasis, lymphatic filariasis, and schistosomiasis. Yet, at least for the treatment of schistosomiasis in children aged less than 5 years, there is no commitment to donate the new medicines. 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. 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 poor medicine delivery that limits the
access to PC for at-risk individuals. For example, pharmacological resistance and limited medicine efficacy warrant the development of better diagnostics and new medicines, whereas poor medicine delivery requires revised government implementation, monitoring, and accounting 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.

The 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, which has improved disease control for more than 1 billion people.\textsuperscript{137} However, the continued expansion of medicine donation programmes is not the only method of increasing or sustaining the treatment of PC-NTDs. The quantity of PC donations now exceeds the capacity of endemic countries to deliver PCs.\textsuperscript{46} Instead, embracing a more comprehensive view of treatment (figure) will result in the more efficient use of existing medicines. There is a need to better target at-risk populations, improve treatment verification, and overturn the view that treatment is synonymous with the availability of PCs.

For MDA, test-and-treat strategies, which require improved rapid diagnostics, might reduce implementation costs in low transmission areas or increase treatment rates of non-compliant populations. More detailed spatial mapping based on disease ecology, especially for focal diseases such as schistosomiasis,\textsuperscript{44} might 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 might reduce the quantity of donated PCs required. These methods to improve the targeting of at-risk populations also might increase patient safety in communities where Loa loa is endemic and PC (ivermectin) cannot be administered en masse.\textsuperscript{46}

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.\textsuperscript{203} Using biometric tools is feasible in low-income countries with ongoing MDA. Currently, the Geshiaro project in Ethiopia, which is led by the London Centre for NTDs and funded by the Children’s Investment Fund, is tracking medicine delivery during MDA with digital fingerprinting. These emerging verification methods could increase the accountability of MDA programmes by reducing data misrepresentation, errors, and incompleteness while also making data immediately available for analysis in local health systems. Disease control can also depend on vector control and water, sanitation, and hygiene.\textsuperscript{573} Without these complementary interventions, MDA might be undermined by high re-infection 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, when appropriate, as well as enhanced accountability and country ownership. Future research should examine how large-scale 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 goals\textsuperscript{57} fast approaching and pharmaceutical commitments heavily aligned with these goals, medicine donation programmes might be curtailed in the near future. Alternative strategies for sustaining the growth of NTD programmes are needed that do not rely on more medicines.

Contributors

All authors reviewed the manuscript and are in agreement with regard to the contents.

Declaration of interests

We declare no competing interests.

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