Neglected tropical diseases: progress towards addressing the chronic pandemic

David H Molyneux, Lorenzo Savioli, Dirk Engels

The concept of neglected tropical diseases (NTDs) emerged more than a decade ago and has been recognised as a valid way to categorise diseases that affect the poorest individuals. Substantial progress in control and elimination has been achieved and policy momentum has been generated through continued bilateral, philanthropic, and non-governmental development organisation (NGDO) support, and donations of drugs from pharmaceutical companies. WHO has defined a Roadmap to reach 2020 targets, which was endorsed by member states in a World Health Assembly Resolution in 2013. NTDs have been included within the Sustainable Development Goal targets and are a crucial component of universal health coverage, conceptualised as “leaving no one behind”. WHO reported that more than 1 billion people in 88 countries have benefited from preventive chemotherapy in 2014. The research agenda has defined the need for affordable products (diagnostics, drugs and insecticides). However challenges such as insecurity and weak health systems continue to prevail in the poorest countries, inhibiting progress in scaling up and also in achieving Roadmap goals.

Introduction
NTDs and the global health agenda
In this Review, we will present progress since the 2010 Lancet Series on neglected tropical diseases (NTDs).1-4 NTDs have been defined as a group of infections strongly associated with poverty in tropical and subtropical environments. NTDs are diverse in biological and transmission characteristics; they predominantly infect populations in low-income and middle-income countries with limited access to health services.5 During the past decade, the momentum to address NTDs has been driven by pledges from pharmaceutical companies to provide free medicines (all on the WHO Essential Medicines list and valued in billions of US$), NGDOs’ commitments to assist implementation of programmes in endemic countries, bilateral support from the US and UK Governments, and an increase in commitment from endemic countries.6 However, despite evidence that interventions to address NTDs are one of the best health investments, only 0·6% of official development assistance for health is provided to NTDs affecting more than 1 billion people. This underinvestment reflects a persistent and continuing inequity in global health financing.7

The London Declaration of 20128 recorded increased commitments of donated drugs for visceral leishmaniasis, lymphatic filariasis, and schistosomiasis, while earlier commitments to provide drugs for fascioliasis, leprosy, leishmaniasis, lymphatic filariasis, onchocerciasis, trypansomiasis, and soil-transmitted helminthiases at no cost to endemic countries were reinforced. In 2013, the World Health Assembly approved Resolution WHA 66.12, which defined strategies for NTDs with clear targets and milestones for 17 NTDs, and endorsed the WHO NTD Roadmap goals linking NTDs to universal health coverage. NTDs are addressed through five strategies: preventive chemotherapy, intensified disease management, vector control, veterinary public health measures for zoonotic neglected diseases, and through improved water and sanitation.8,9

Momentum for further investment came in 2015 with the inclusion of NTDs within the health targets of the Sustainable Development Goals (SDGs)10 when the Global Fund Board11 agreed to support interventions that addressed co-infection and co-morbidities and the G7 Heads of State recognised NTDs as a major challenge emphasising the need to support research and interventions.12 An agreed SDG target was to reduce the number of people accessing NTD interventions by 90% by 2030. However, the burden of NTDs is heavy on the poorest people in G20 countries (together with Nigeria) and if these countries implemented NTD programmes then a high proportion of the NTD burden could be resolved.13

Increased investment for NTDs will improve the wellbeing of vulnerable groups, which together with improvements in water, sanitation, hygiene, and education, are appropriate links to many of the SDGs. NTDs define poverty in many settings and have been described as litmus tests of progress in poverty alleviation, or are described as markers of poverty.14

NTD partnerships: evolution and expansion from disease-specific to a wider context
Disease-specific partnerships represent the diversity of communities involved in NTDs and have made a major contribution to scaling up of programmes. NGDO commitment was pioneered by NGDOs that supported the delivery of ivermectin for onchocerciasis control and multidrug therapy for leprosy elimination programmes.15 Since 2010, new partnerships have emerged to coordinate and advocate for particular conditions (table). Disease-specific alliances generate opportunities for advocacy and increased resources from non-traditional donors, and reflect the need to facilitate interaction between endemic countries, international organisations, non-governmental organisations, pharmaceutical donors, philanthropic foundations, and academia.
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<tr>
<th>Latest WHO resolutions, year</th>
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<tr>
<td></td>
<td>DALYS (million)</td>
<td>Deaths per year</td>
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<td>2015/2017</td>
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<td><strong>All NTDs</strong></td>
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<tr>
<td>WHA66.12, 2013</td>
<td>47.90</td>
<td>152,000</td>
<td>WHO Roadmap</td>
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<td><strong>Viruses</strong></td>
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<tr>
<td>Dengue and dengue haemorrhagic fever</td>
<td></td>
<td></td>
<td>Sustainable vector control interventions established in 10 high priority countries</td>
<td>Dengue control and surveillance systems established in all regions, number of cases reduced by 25% (2009–10 baseline) and deaths by 50%</td>
<td>Dengue Vaccine Initiative, Paediatric Dengue Vaccine Initiative, Innovative Vector Control Consortium (IVCC)</td>
<td>100</td>
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<tr>
<td>WHA 55.17, 2002</td>
<td>0.83</td>
<td>3000–4200</td>
<td></td>
<td></td>
<td></td>
<td>Improve availability of vaccine, diagnostics; epidemiological situation of dengue in Africa; capacity for case management and vector control</td>
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<tr>
<td>WHA 20.20, 1950</td>
<td>1.46</td>
<td>26,000 (other sources 55,000)</td>
<td>Eliminate human rabies transmitted by dogs and dog-to-dog transmission in all endemic areas in Latin America, intensified control and enhanced surveillance should lead to 50% reduction in number of human rabies deaths by 2015</td>
<td>Eliminate human rabies transmission by dogs and dog-to-dog transmission in all affected countries in WHO's South-East Asia and Western Pacific regions</td>
<td>Global Alliance for Rabies Control</td>
<td>150</td>
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<td><strong>Protozoa</strong></td>
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<td>Chagas' disease</td>
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<td>Interrupt transmission via intradomiciliary vectors in Latin America and transmission via blood transfusion in Latin America, Europe and the western Pacific</td>
<td>Elimination in 100% of foci</td>
<td>Global Chagas’ Coalition, Drugs for Neglected Diseases Initiative (DNDi)</td>
<td>21 in Americas</td>
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<tr>
<td>WHA51.14, 1998</td>
<td>0.55</td>
<td>10,300</td>
<td></td>
<td></td>
<td></td>
<td>Improved diagnostic and therapeutics to treat chronic disease; implementation of intradomiciliary vector control</td>
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<td>Human African trypanosomiasis</td>
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<td>2000–3000 cases per year reported, enhance vector patient accessibility; elimination of disease in 80% of foci</td>
<td>Elimination in 100% of foci</td>
<td>Pan-African Programme for Trypanosomiasis Eradication and Control; Drugs for Neglected Diseases Initiative (DNDi); Fund for Initiative Diagnostics (FIND)</td>
<td>36</td>
</tr>
<tr>
<td>WHA57.2, 2004</td>
<td>0.56</td>
<td>9100</td>
<td></td>
<td></td>
<td></td>
<td>Improved diagnostics, oral therapy for both early and late stage disease; scale-up of use of tiny targets for vector control; for acute disease in Uganda, implement chemotherapy of cattle and selective application of insecticide to cattle</td>
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<td>Leishmaniases</td>
<td></td>
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<td>WHA60.13, 2007</td>
<td>3.32</td>
<td>–</td>
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<tr>
<td>Visceral Indian sub-continent</td>
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<td></td>
<td>100% case detection and treatment, with &gt;1 case per 10,000 population at district and sub-district levels</td>
<td>–</td>
<td>Drugs for Neglected Diseases Initiative (DNDi)</td>
<td>19 in Americas, east Africa, and Asia</td>
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<tr>
<td>–</td>
<td>–</td>
<td>51,600</td>
<td></td>
<td></td>
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<td>Implement defined strategy; increase access to liposomal amphotericin B and implement vector control based on documented status of resistance of vector populations</td>
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<td>2020</td>
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<tr>
<td>Cutaneous</td>
<td>No deaths</td>
<td>70% of all cases detected and at least 90% of all detected cases treated in the Eastern Mediterranean Region</td>
<td>Drugs for Neglected Diseases Initiative (DNDi)</td>
<td>No data available, although increased incidence reported throughout area of conflict in Middle Eastern region</td>
<td>Continue search for improved drugs to treat cutaneous and mucocutaneous disease; improve if possible access of populations to therapy in conflict areas; implement reservoir control programmes to reduce animal reservoir</td>
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<tr>
<td>Helminth</td>
<td>No data</td>
<td>No data</td>
<td>Interventions scaled up in selected countries for Taenia solium taeniasis/ cysticercosis control and elimination</td>
<td>No data</td>
<td>Taenia infections can be treated with praziquantel but no standard treatment exists for NCC, individual case treatment with praziquantel or albendazole or both, antiepileptic drugs, or corticosteroids</td>
<td>Implement pilot projects to evaluate strategy; engage veterinary, sanitation and food safety sectors to reduce disease burden—will require combination of tools (albendazole treatment or vaccination of pigs to prevent or cure porcine cysticercosis); pig vaccine expected to receive regulatory approval in India</td>
</tr>
</tbody>
</table>

* WHO: World Health Organization; NCC: neurocysticercosis; DALYS: disability-adjusted life years; DNDi: Drugs for Neglected Diseases Initiative.
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<tr>
<td><strong>Echino-coccosis</strong></td>
<td>0.14</td>
<td>1200</td>
<td>Pilot projects to validate effective strategies where disease is a public health problem (eg, major burden in China)</td>
<td>Validated strategy available for echino-coccosis/hydatidosis and interventions scaled up in selected countries for their control and elimination</td>
<td>Implement pilot strategy in areas of high risk</td>
</tr>
<tr>
<td><strong>Foodborne trematodes</strong></td>
<td>1.88</td>
<td>7000 (reported in 2005 but not by GBD study)</td>
<td>75% of population at risk of infection reached by preventive chemotherapy; morbidity controlled in all endemic countries</td>
<td>17 Reduced numbers of cases reported in Egypt of fascioliasis; increased treatments for fascioliasis in Peru and Bolivia since 2009; increased treatment programme for opisthorchiasis in Laos and in Vietnam for clonorchiasis; mapping of areas of endemicity in Cambodia and initiation of treatment programme</td>
<td>Define extent of endemic areas; develop serological and molecular methods for improved diagnosis; increase access to praziquantel (or triclabendazole for fascioliasis); engage with other sectors to reduce risk via health education and improved sanitation</td>
</tr>
<tr>
<td><strong>Lymphatic filariasis</strong></td>
<td>2.78</td>
<td></td>
<td>By 2017, 70% of all 81 endemic countries will have met the criteria to stop interventions and entered the post-intervention surveillance phase</td>
<td>100% of all endemic countries will have been verified as free of transmission or will have entered post-intervention surveillance</td>
<td>Implement albendazole 2 times per year in Loa loa co-endemic areas with vector control via impregnated bednets; scale-up interventions in newly defined endemic areas; assess impact of onchocerciasis programmes on filariasis endemicity and impact of lymphatic filariasis programmes on soil-transmitted helminthiases; develop a short duration macrofilaricide based on anti-wolbachia antibiotics as a substitute for doxycycline; complete triple therapy trials; increase efforts to address morbidity</td>
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### Latest WHO resolutions, year

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<tr>
<td>Onchocerciasis</td>
<td>WHA62.1</td>
<td>0.49 No deaths attributed</td>
<td>Elimination in Latin America and Yemen</td>
<td>Organization for Elimination of Onchocerciasis in the Americas (OEPA); African Project for Onchocerciasis Control APOC (closed end of 2015) and New Expanded Special Project for Elimination of NTDs Africa</td>
<td>37 countries previously had varying levels of endemicity post-control: Colombia, Ecuador, and Mexico now verified as free of transmission; Guatemala has submitted documents to verify elimination of transmission; overall, 132 million/172 million total population estimated to require treatment (65.3% global coverage); progress towards nationwide elimination in Burundi; Chad, Guinea Bissau, Kenya, Malawi, Mali, Niger, and Senegal; fiscal elimination in 6 countries (Cameroon, Ethiopia, Nigeria, Sudan, Tanzania, Uganda) achieved but in Cameroon difficulties exist in areas of high transmission zones co-endemic with Loa loa; Northern focus in Venezuela under surveillance while southern focus cross-border Brazil/Venezuela using ivermectin 4 times per year or doxycycline to reduce transmission; new infected Yanomami communities found.</td>
<td>Develop a short duration macrofilaricide based on anti-wolbachia antibiotics as a substitute for doxycycline; implement ivermectin 2 times per year strategy for control or elimination in Africa; define areas of low transmission; define areas where transmission has been arrested by implementation of new WHO guidelines.</td>
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<tr>
<td>Schistosomiasis</td>
<td>WHA 65.21</td>
<td>3.31 11700</td>
<td>Regional elimination as a public health problem in eastern Mediterranean, Caribbean and Indonesia and Mekong basin</td>
<td>Global Schistosomiasis Alliance</td>
<td>–</td>
<td>In 2013, 47 million individuals of 261 million requiring treatment reached; in 2014, 61.4 million school-age (5-14 year-olds) and adult individuals treated—20% of those needed. Praziquantel available as donated drug with 250 million donated tablets being available in 2016; donors purchasing additional praziquantel.</td>
<td>Develop paediatric praziquantel formulation; define link between HIV and urogenital schistosomiasis to evaluate risk of HIV transmission.</td>
</tr>
<tr>
<td>Soil-transmitted helminthiases</td>
<td>WHA54.19</td>
<td>5.19 2700</td>
<td>50% of people in need of preventive chemotherapy, including children (preschool-aged and school-aged children) are regularly treated in 100% of endemic countries</td>
<td>STH Coalition managed by Children Without Worms</td>
<td>–</td>
<td>Number of school-age children treated has increased from 200 million in 2010 to 271 million in 2014 (40% of estimated 576 million children at risk); in 2014, 138 million of 269 million pre-school children estimated to be in need of treatment were treated (global coverage of 51.4%); in 2016, India treated 140 million children through a school-based deworming programme in a single day, and in 2014 Egypt treated 2 million school-age children over a 4 week period.</td>
<td>Evaluate value of treating adults if transmission is to be interrupted; develop drug efficacy monitoring at scale; evaluate new products or combinations; improve diagnostic tools.</td>
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Note: DALYS ( Disability Adjusted Life Years) and Deaths per year.
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<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td><strong>Global Buruli Ulcer Initiative</strong></td>
<td><strong>33</strong></td>
<td><strong>12/15</strong> countries that report regularly 2020 new cases in 2014 compared with 5000 in 2009</td>
<td><strong>Rapid point of care diagnostic</strong></td>
<td></td>
</tr>
<tr>
<td>Buruli ulcer</td>
<td>WHA57, 2004</td>
<td>5000–6000 cases per year</td>
<td>Oral antibiotic therapy incorporated into control and treatment 70% of cases detected early and cured with antibiotics in all endemic countries</td>
<td>Global Buruli Ulcer Initiative</td>
<td></td>
<td></td>
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<tr>
<td>Leprosy</td>
<td>WHA44, 1991</td>
<td>0.006</td>
<td>No deaths attributed</td>
<td>International Leprosy Elimination Programme</td>
<td></td>
<td></td>
<td><strong>Focus on countries with continuing high prevalence</strong></td>
</tr>
<tr>
<td>Trachoma (avoidable blindness)</td>
<td>WHA62, 2009</td>
<td>0.33</td>
<td>No deaths attributed</td>
<td>International Trachoma Initiative and GET 2020</td>
<td></td>
<td></td>
<td><strong>Implement expanded trichiasis surgery</strong></td>
</tr>
<tr>
<td><strong>Yaws/endemic treponematoses</strong></td>
<td>WHA2.6, 1949</td>
<td>Not calculated</td>
<td></td>
<td>Global eradication</td>
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<tr>
<td><strong>Non-infectious NTDs</strong></td>
<td></td>
<td></td>
<td><strong>Global Snake Bite Initiative</strong></td>
<td></td>
<td></td>
<td><strong>Production of antivenom stopped by manufacturers and no safety or quality alternatives available for common snakebite in Africa</strong></td>
<td><strong>Develop polyvalent antivenom not needing cold chain, advocate for greater attention to snake bite as cause of mortality</strong></td>
</tr>
<tr>
<td>Snake bite</td>
<td></td>
<td>96 000 per year</td>
<td></td>
<td>Global Snake Bite Initiative</td>
<td></td>
<td></td>
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<tr>
<td>Podoconiosis</td>
<td></td>
<td>No deaths attributed</td>
<td></td>
<td>International Podoconiosis Initiative (Footwork)</td>
<td></td>
<td><strong>Increased recognition of problem over recent years, definition of areas of endemicity</strong></td>
<td><strong>Implement morbidity management</strong></td>
</tr>
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</table>

Data are derived from various sources.6,8,46,52,53,57 MDA=mass drug administration. UIG=ultimate intervention goal. *Global Burden of Diseases, Injuries, and Risk Factors Study 2010 data.

Table: Neglected tropical diseases and the associated global burden, targets, partnerships, endemic countries, treatment progress, and research needs
Science underpinning the NTD case
The burden of NTDs
The Global Burden of Disease study of 20107 attributed some 27 million disability-adjusted life years (DALYs) to NTDs. A 2014 study8 included other conditions not included within the WHO official NTD list of 17 diseases, and attributed 47.9 million DALYs to all NTDs; another study9 in 2009 estimated the burden for NTDs was 56 million DALYs. The global annual mortality from NTDs was reported as around 150 000 deaths per year by the Global Burden of Disease study.10 However, this estimate excluded deaths from rabies (55 000 deaths), snakebite (up to 94 000 deaths), cancers associated with trematode infections (60 000 deaths), and neurological NTD conditions such as neurocysticercosis-related epilepsy (60 000 deaths)—these deaths are also included in other categories. These figures suggest the total annual mortality from NTDs is actually around 350 000. In 2010, WHO reported that schistosomiasis mortality alone could be as high as 280 000 per year in Africa—a 20-fold difference from the official GBD data.11 Morbidity from permanent blindness, debilitating skin disease, disability and disfigurement with long term psychological and social and economic consequences will elevate the total DALY burden but are not included in Global Burden of Disease metrics.12

NTD comorbidities: HIV, epilepsy, and cancer
A possible association between HIV and urogenital schistosomiasis has been recognised. Ndeffo Mbah and colleagues13 showed increased HIV positivity in females infected with Schistosoma haematobium. The opportunity to reduce the risk of HIV in young females (5–15 years) associated with S haematobium urogenital pathology by annual praziquantel has yet to be recognised by the HIV community, despite the need to achieve high coverage of this at-risk group irrespective of a direct link to HIV. The safety of praziquantel has been reconfirmed during pregnancy and lactation.14 The longstanding policy to assure coverage of young females with praziquantel treatment should be implemented by both the NTD and HIV constituencies. Neurocysticercosis infection caused by Taenia solium cysts has been associated with epilepsy and estimates suggest some 30% of global epilepsy is associated with neurocysticercosis.15 Bladder cancer associated with S haematobium and food-borne trematode infections that cause cholangiocarcinoma are estimated to cause 60 000 deaths annually.16 The successful schistosomiasis control programme in Egypt has seen a rapid decline in bladder cancer during the past 2 decades.17 Comorbidities associated with hookworm and schistosomiasis also exacerbate malaria pathology, particularly in pregnancy, which reduces birthweight and increases risk of neonatal and infant mortality. Further, the mental health comorbidity of many NTDs and the impact these conditions have on the psycho-social status of individuals and families, particularly depressive illness and anxiety of patients with NTDs as well as caregivers has only recently been highlighted as a problem with significant additional burden.18

Definition of research priorities
Research priorities for NTDs have been published in a series of reports by WHO and the Special Programme for Research and Training in Tropical Diseases, outlining priorities for kinetoplastid parasites (trypanosomes and leishmanias), helminth infections, zoonoses and viral infections (dengue, and other arboviruses).19 A consensus has been reached that new drugs, insecticides, and diagnostics are required, which will offer improved and cost-effective therapies, vector-control tools, and diagnostics. Attempts to develop vaccines for multicellular parasites are yet to develop a product for large-scale use. However, progress to address the expanding dengue threat has been made with the development of a vaccine for dengue (Dengvaxia, Sanofi Pasteur, Lyon, France). Dengvaxia has been licenced in Mexico for use in highly endemic areas, after results of safety and efficacy studies in clinical trials showed reduced incidence of hospitalisation in vaccinated children aged 2–16 years old in three clinical trials involving 35 000 children.20

Research to improve delivery of existing products and evaluate efficacy of existing therapeutics will be necessary, as will exploration of combinations of products known to be effective. Specific research priorities are improved oral therapy for human African trypanosomiasis that is effective in both early and late stage disease; and improved chemotherapy for leishmaniasis, Chagas’ disease, and buruli ulcer—current therapies are not ideal owing to the duration of required treatment, mode of administration, and toxicity. A short-duration macrofilaricidal treatment to kill or permanently sterilise adult filarial worms is still needed, because despite the efficacy of the anti-Wolbachia antibiotic, doxycycline, the duration of treatment and eligibility criteria currently restrict its widespread use. Praziquantel has been donated for mass drug administration in school-aged children for schistosomiasis; however, it needs to be reformulated for paediatric use given that pre-school children are frequently infected. The combination of praziquantel with artesunate for treatment of both adults and juvenile forms of schistosomes might be considered.21

Research linked to implementation of programmes and challenges that programmes face as they mature require social science involvement to improve coverage and adherence, and improved methodologies to evaluate impact and address problems identified in acceptability and coverage.22 Research to understand interactions between social networks within communities could help ensure optimum understanding and uptake of drugs.23 Increasingly complex and diverse research questions have emerged as programmes dependent on mass drug administration have progressed. Such questions
relate to the duration and frequency of mass drug administration for different diseases, the broad spectrum effectiveness of the anthelminthics used and the impact of vector control on transmission of filariasis.31

Mapping disease distribution
Accurate mapping of disease distribution is a prerequisite for effective implementation. Onchocerciasis programmes have shown the importance of defining endemicity; in these programmes, levels of endemicity were defined by rapid epidemiological assessment and mapping.13 The serious adverse events associated with Loa loa co-endemcity with onchocerciasis meant a rapid mapping methodology was required to define areas of highest risk.13 Similar rapid mapping using antigen detection methods are used to identify where lymphatic filariasis mass drug administration should be instituted.14 The need to know the distribution of NTDs that can be controlled or eliminated by preventive chemotherapy led to the development of online resources to ensure all requisite data are available and updated. The Global Trachoma Mapping Project is an example of how mobile phone and geographic information system technologies can be used: population-based prevalence surveys are done in all districts where trachoma is suspected to acquire data on burden and risk, thus enabling prioritisation of interventions and policy determination for implementation of the surgery, antibiotics, facial cleanliness, and environmental improvement (SAFE) strategy.15 Detailed mapping of foci of human African trypanosomiasis due to Trypanosoma brucei gambiense infection has defined areas of highest risk for active surveillance.16

Use of remote sensing technologies to produce datasets that precisely define zones of climate (rainfall indices, cloud cover), physical parameters (altitude, soil type), and ecological parameters (forest cover, vegetation type) is increasingly important, as predictors of disease ecology reflecting drivers of transmission of vector borne infections. Definable physical characteristics such as soil type are associated with podoconiosis distribution.15 The NTD global mapping tool provides an interactive means to assist the planning and implementation of preventive chemotherapy for NTDs, enabling visualisation of geographical distribution of diseases and the priority areas requiring mass drug administration where co-implementation should be initiated. The global mapping tool also complements the Global Atlas of Helminth Infections, provides information on water and sanitation, and allows progress of interventions to be tracked.

The need for alternative strategies—the operational research agenda
Some preventive chemotherapy programmes require alternative strategies to reach elimination targets, which need to be piloted and implemented. These alternative strategies include: ivermectin twice a year for filariasis in Africa; albendazole twice a year for lymphatic filariasis in L loa co-endemic areas; bednet coverage to eliminate lymphatic filariasis; and the use of doxycycline as a macrofilaricide or ivermectin four times per year in some areas of onchocerciasis endemicity, such as in Brazil and Venezuela.13,14 Thomsen and colleagues15 examined a triple combination of diethylcarbamazine, albendazole, and ivermectin for filariasis and showed that microfilaria levels remain suppressed for a 24 month period thus providing an opportunity to reduce the frequency of mass drug administration in areas where onchocerciasis is not co-endemic.

Additionally, to reduce the problem of the limited effect of albendazole on trichuris infections, ivermectin should be considered; however, ivermectin is not donated for trichuris infections or for scabies. Because extensive insecticide resistance exists in Africa, the value of bednets to eliminate Wuchereria bancrofti transmission needs to be reassessed.40

Cochrane systematic reviews: the deworming debate
In 2015, the Cochrane Collaboration challenged the benefits of deworming for the control of soil-transmitted helminthiases after their analysis41 of randomised controlled trials (RCTs). This finding provoked robust debate42 about whether RCTs are an appropriate way to measure the nutritional and educational benefits of preventive anthelminthic chemotherapy. Most RCTs do not take into account that recovery from nutritional deficits is a process that takes much longer than 1 year, especially if the quality and quantity of the nutrients assumed in the diet are limited.

Furthermore, a significant proportion of individuals treated with preventive chemotherapy are uninfected but are nevertheless treated for logistical reasons and thus no nutritional benefits are expected to accrue in this group. RCTs normally calculate the mean benefit of preventive chemotherapy on the entire treated group but the true benefits are obtained only by those infected and are therefore greatly diluted.

Additionally, different worm species have different pathological effects—hookworm causes anaemia, ascariasis retards growth—hence when the results of preventive chemotherapy are evaluated it is important to recognise which species of soil-transmitted helminthiases are removed. For example, an improvement in haemoglobin levels should not be expected if hookworms are not the prevalent species in the population treated. On the basis of the evidence from all studies including RCTs, WHO issued a consensus statement reiterating the justification of the present policy of preventive chemotherapy.44 Provision of deworming to infected populations reflects equity and ethical aspects and the intervention is recognised to reinforce the trust in the health and education service, aspects that the Cochrane systematic review of RCTs is unable to evaluate.
Progress towards Roadmap goals

Progress on specific diseases

Substantial progress towards WHO Roadmap goals and regional targets has been achieved since 2010 (table). The Uniting to Combat NTDs initiative tracks progress on ten NTDs towards the agreed targets against a scorecard that is published annually.

Dracunculiasis (Guinea worm disease)

Since the introduction of the Guinea Worm Eradication Programme in 1986, 16 countries have been certified free of Guinea Worm transmission, including 6 countries since 2010 (Burkina Faso, Côte d’Ivoire, Ghana, Niger, Nigeria, and Togo). However, four countries remain endemic—Chad, Ethiopia, Mali, and South Sudan—who reported only 22 cases in 2015 compared with 126 cases in 2014.4 Each of these endemic countries pose different challenges if transmission cessation is to be confirmed. A possible cycle of transmission that involves dogs, fish, and amphibians as paratenic hosts was discovered in Chad, meaning a change in approach could be required because 503 dog infections were recorded in Chad in 2015; from January, to June, 2016, 498 dogs have been reported infected and four human cases have been identified in Chad. Human cases were also reported in South Sudan and Ethiopia in June, 2016.44 In Mali, access to endemic areas is curtailed due to insecurity. In South Sudan, strong progress has been made to reduce the numbers of infected villages but problems of access, population movement, cattle camps, and insecurity pose end-game challenges.

Human trypanosomiases

Achievement of the target to reduce the number of chronic human African trypanosomiases cases to between 2000–3000 cases per year by 2015 is close: WHO reported 3796 cases in 2014 and less than 3000 in 2015. This figure was the lowest reported incidence for 75 years and was achieved by active surveillance of defined high-risk foci and donation of products for chronic human African trypanosomiases therapy (pentamidine and nifurtimox-eflornithine).45 The availability of tiny insecticide impregnated targets for glossina control, 46 new diagnostic tests, and the prospect of an oral therapy to treat both phases of the disease—fenoxidazole, which is now in phase 2 and 3 trials calls for optimism.

Chemotherapy for Chagas’ disease remains problematic; less than 1% of patients have access to benznidazole. Despite an impact on parasite serological parameters, a randomised trial of benznidazole did not significantly reduce levels of cardiac clinical deterioration through 5 years of follow-up.47

Leprosy

215 656 new cases of leprosy were reported in 2013 in 103 countries. During the past 20 years, more than 14 million patients have been cured of the disease, 4 million since 2000. The prevalence of leprosy has dropped by 90%: from 21·1 per 10 000 people in 1983 to less than 0·24 per 10 000 people in 2014. A substantial decrease in the global disease burden has been achieved; the number of leprosy cases has reduced from 5·2 million in 1985, to 180 618 cases at the end of 2013, which has led to the suggestion that the public health problem has been eliminated—defined by WHO as a prevalence of less than 1 case per 10 000. However, although the problem of leprosy has been reduced by multidrug therapy, pockets of high endemicity remain in several countries, including India, Brazil, and Indonesia, therefore this ancient and stigmatising disease should remain an priority.48

Lymphatic filariasis

In 2014, 73 countries remained endemic for lymphatic filariasis; 18 countries are now entering the surveillance phase but 11 countries have not yet commenced mass drug administration programmes. Some 23 countries have only implemented limited mass drug administration and have not reached 100% geographical coverage. Countries that have not achieved complete coverage will not be able to reach the 2020 target of elimination. However, 18 countries have moved into a surveillance phase following transmission assessment surveys, an evaluation which suggests transmission has been arrested.49 However, The Gambia appears to have eliminated transmission, without the introduction of mass drug administration, with long-term use of impregnated bednets for malaria control.50 A 2014 estimate of the impact of mass drug administration during the past 13 years suggests more than 96·71 million cases of lymphatic filariasis were prevented or cured; yet 36 million cases of hydrocoele and lymphoedema remain.51 The economic benefits estimated to have accrued during the first 8 years of the programme exceed $24 billion. In 2014, 559 million people were treated for lymphatic filariasis and the cumulative number of treatments reported was 5·62 billion to more than 1 billion individuals.52

The filariasis test strip, which is based on the immune-chromatographic test, has been introduced as an improved method for use in mapping and evaluation.53 This test will be used for transmission assessment surveys to determine the impact of mass drug administration and allow for decision making with regard to cessation or to evaluate any recrudescence. Lymphatic filariasis accounts for at least 2·8 million disability-adjusted life-years;54 this figure does not include the substantial comorbidity of mental illness commonly experienced by patients and their caregivers.55 For WHO’s Global Programme to Eliminate Lymphatic Filariasis to succeed, 100% geographical coverage of both mass drug administration and patient care is necessary and could be achieved through the implementation of morbidity management and surgery.56
**Onchocerciasis**

Three countries have been verified as free of transmission of *Onchocerca volvulus*: Colombia, Ecuador, and Mexico. Guatemala has submitted a dossier that indicates that transmission has stopped in all the previous endemic foci, while the northern focus in Venezuela is under post-control surveillance. However, the cross-border focus straddling Brazil and Venezuela exemplifies challenges of remote areas; migratory Yanomami groups who require treatment characterise the difficulties of sustaining ivermectin distribution four times per year. Some infected individuals who remain positive have been hospitalised for treatment with the macrofilaricide doxycycline.

Closure of the African Programme for Onchocerciasis Control at the end of 2015 and the creation of the Expanded Special Project for the Elimination of NTDs in Africa for the control of other preventive chemotherapy-targeted NTDs will transfer the responsibility to provide technical support to country programmes to the WHO Regional Office for Africa. The African Programme for Onchocerciasis Control delivered more than 1 billion treatments between 1997 and 2014 in 19 countries, built capacity through training or retraining of more than 148 000 health workers and 1·46 million community directed distributors, facilitated use of community structures for other health programmes, and empowered more than 190 000 communities to direct their own ivermectin treatment schedules.

The African Programme for Onchocerciasis Control made epidemiological progress towards nationwide elimination in Burundi, Chad, Guinea Bissau, Kenya, Malawi, Mali, Niger, and Senegal. Focal elimination in six countries (Cameroon, Ethiopia, Nigeria, Sudan, Tanzania, and Uganda) was achieved, but in Cameroon there are difficulties in high transmission zones that are co-endemic with *L. loa*. In such zones, coverage and adherence are inadequate to satisfy the expectation that transmission can be arrested without implementation of additional strategies.

**Scabies**

Scabies is caused by the ecto-parasitic mite *Sarcoptes scabiei* and is highly susceptible to ivermectin, which is used in onchocerciasis and lymphatic filariasis programmes. The results of a study in Fiji showed efficacy of ivermectin for scabies compared with standard treatments of topical permethrin cream. The lack of data on the impact of ivermectin on scabies after nearly 3 decades of use in mass drug administration programmes is a major deficit, representing a missed opportunity.

**Schistosomiasis**

The World Health Assembly resolution of 2012 (WHA 65.21) called for the elimination of schistosomiasis and reinforced the importance of regular treatment of at least 75% of school age children in areas at risk of both schistosomiasis and soil-transmitted helminthiasis as stated in a previous resolution (WHA 54.19). Schistosomiasis programmes will now benefit from the increased donation of praziquantel, because from 2016, 250 million tablets equivalent to 100 million treatments will be available. The number of school-age children treated in 2014 was 49·2 million, equivalent to 34.6% of global coverage for this age group. In spite of this significant progress, scale-up remains slow in the highest burden countries where 70% of the burden occurs. If the elimination goals for schistosomiasis are to be met, endemic countries should define high priority intervention areas, access the available donated drug, implement health education messages to emphasise the importance of safe water and sanitation provision in reduction of transmission, and recognise the importance of pre-school age children and their need for treatment if possible with a paediatric formulation of praziquantel. The association between HIV and urogenital schistosomiasis requires resolution with strong policy enforcement through the regular treatment of school girls, women of childbearing age, and throughout pregnancy and lactation as recommended by WHO and the original manufacturers of praziquantel.

**Soil-transmitted helminthiasis**

Between 2008 and 2013, the number of children treated for soil-transmitted helminthiasis doubled. WHO reported that 440 million pre-school and school-age children were treated in 2014 with anthelmintics (albendazole and mebendazole)—rates of coverage have increased since 2008 and a global coverage of 44–51% has been achieved. The figures for treatment of soil-transmitted helminthiasis do not include individuals receiving anthelmintics via filariasis and onchocerciasis programmes that treat adults as well as younger age groups. The need to treat adults is recognised, if a permanent reduction in transmission is to be achieved, as well as the importance of the role of the water, sanitation, and hygiene sector to sustain the gains regular deworming can provide.

**Trachoma**

The SAFE strategy for the elimination of trachoma with its four components—surgery, antibiotics, face washing, and environment—shows the multiple approaches required if public health goals are to be achieved. The Global Trachoma Mapping Project provided detailed information for implementation of mass drug administration using azithromycin, identified where the burden of trichiasis is highest for prioritisation of surgery, and identified where implementation of the face washing and environment components of the SAFE strategy will pose the greatest challenge. The implementation of mass drug administration in all endemic districts at 80% coverage for 3–5 years, depending on prevalence of active trachoma, will pose a...
significant challenge notwithstanding the estimated backlog of 5 million cases of trichiasis surgery; Solomon has emphasised the benefit of improved trichiasis surgery technique in reducing recurrence of trachoma.

**Yaws**

Yaws (*Treponema pallidum pertenue*) is a disabling skin condition that has been identified as a potential eradication target on the basis of oral azithromycin efficacy. WHO developed the Morges Strategy for Yaws Eradication by 2020, the strategy will involve mass drug administration of single dose azithromycin to entire endemic communities, supported by surveillance until clinical cases are no longer detected, and by treatment of all active cases and their contacts. Pilot interventions have been initiated in several countries: in Nsukka, Nigeria, mass drug administration with oral azithromycin interrupted transmission within 6–12 months. In India, after a 20 year campaign using penicillin injection followed by sero-surveillance of children for treponemal antibodies, WHO reported that yaws was no longer present in India and declared its eradication (technically elimination).

**Implementation strategies requiring collaboration with other sectors**

**Vector control**

Vector control has been a major component of NTD programmes over many decades. Many NTDs such as lymphatic filariasis, visceral leishmaniasis, onchocerciasis, and Chagas' disease have benefited from vector control. Additionally, new approaches to the control of human African sleeping sickness using tiny target technology or selective spraying of cattle to control the acute zoonotic form of disease have been shown to be effective interventions but require implementation at scale.

Development of novel tools and methods to curb the spread of (day-biting and outdoor-biting) *Aedes aegypti* mosquitoes that transmit dengue and Chikungunya is a high priority, reinforced by the emergence of Zika virus. Development of novel vector control methods will require substantially increased investment if they are to be implemented. Increasing levels of resistance to present pyrethroid-based insecticides threaten the progress of the lymphatic filariasis elimination programme in Africa. Global warming, climate change, unplanned urbanisation, and global travel of people and goods, will have an impact beyond the traditional populations associated with NTDs. The establishment of schistosomiasis in Corsica exemplifies these threats; small populations have been found in Corsica that are susceptible to infection with a parasite strain from Africa, a hybrid of *S haematobium* and *Schistosoma bovis*, therefore these strains could become established in southern Europe.

Neglected zoonotic diseases: the One Health concept

Neglected zoonotic diseases occur in many settings, caused by diverse groups of organisms, hence generalisations about approaches to their control is difficult. However, progress has been made to define strategies for control of specific diseases, which require an approach that goes beyond the health sector. The vision for One Health is a culture change that recognises the importance of the link between humans, animals, and ecosystems, providing added value by translation of the One Health approach into zoonotic disease control. Successful application of One Health strategies are the use of dog vaccination in the control of human rabies in Latin America, KwaZulu-Natal, the Philippines, and Bali, and the control of the acute form of human sleeping sickness, *Trypanosoma brucei rhodesiense*, in south east Uganda. In Uganda, chemotherapy of the cattle reservoir, together with vector control by spraying of cattle to selectively kill the tsetse fly *Glossina fuscipes*, has been shown to effectively reduce the incidence of sleeping sickness cases. The One Health approach can also be applied to the control of cysticercosis and echinococcosis, globally distributed cestode infections, in which interventions focused on animal reservoirs (pigs and dogs) are essential components of interventions to reduce human prevalence allied to behaviour change and curative therapy.

**Water, sanitation, and hygiene**

Sustained control and elimination of soil-transmitted helminthiases and schistosomiasis, require not only chemotherapy, but also access to clean and safe water together with appropriate waste disposal and behaviour changes to reduce transmission. However, provision of clean and safe water in the more remote areas where NTDs and other waterborne infections are most prevalent poses a substantial challenge and the involvement of other sectors is required. Engagement of the water, sanitation, and hygiene sector and the inclusion of NTDs within this framework, reflects a holistic policy approach within the SDG goals.

**Place of NTDs in the global health context towards 2030**

During the past decade, NTDs have attracted increased attention and investment. Availability of drugs is no longer a barrier to achievement of universal health coverage for most NTDs yet they remain a chronic pandemic in the poorest sectors of society in endemic countries who now have access to donated drugs. Further progress will be driven by commitment of countries to contribute to the relatively small costs of delivery—estimated at 1–3% of national health budgets—to ensure access to donated products with a calculated annual value of $2–3 billion. In 2015, 1·1 billion people received preventive chemotherapy, representing a public health success, and 140 million children were dewormed in a single day in February, 2016, in India. However, progress towards achievement of the 2020 WHO Roadmap targets has been patchy. The resources allocated to NTDs are not yet adequate to address the totality of the problem.
estimated requirements to achieve Roadmap goals are double the current $300 million annual funding provided. However if vector control is included the estimated amount required would be ten times that amount. The challenge is to persuade endemic countries to invest national resources to develop robust and dependable health delivery systems to ensure the gains from NTD control or elimination are translated into long-term human development gains.

NTDs are tracers of equity in progress toward other SDGs and targets, including universal health coverage (target 3.8), access to safe water (target 6.1), and sanitation (target 6.2). NTD endemic populations are the least likely to have access to such services, hence use of NTDs as an indicator of progress is a logical step to justify these diseases in the SDG targets. Other SDG goals upon which NTD interventions and partnerships are relevant are education (target 4), gender equality (target 5), decent work and economic growth (target 8), reduced inequalities (target 10), sustainable cities and communities (target 11), climate action (target 13), and partnership for the goals (target 17). The most recent WHO and World Bank report on monitoring of universal health coverage is explicit that “monitoring preventive chemotherapy remains key to ensuring that the diseases of the least well-off are being prioritised from the very beginning of the path to UHC”.

However, additional challenges exist with respect to implementation as well as the need for a new generation of products: countries have limited human resources; some populations are difficult to access; civil unrest and conflict impede implementation; drug resistance and insecticide resistance could develop; and environmental change impacts on the ecology and behaviour of vectors. Additionally, the value of quantitative and mathematical modelling approaches to inform policy decisions for a group of NTDs has been emphasised through the work of the NTD Modelling Consortium.

A 2016 study on health gains from NTD programmes has estimated that 175 million DALYs have been averted in the 15 years of the lymphatic filariasis programme, while if targets are met for nine NTDs 600 million DALYs would be averted, which can be extrapolated to 2030 largely due to the decline in morbidity of NTDs treated by preventive chemotherapy. However, this figure does not estimate for gains in sub morbidities through improved cognitive development and mental health and only nine NTDs were used in the calculation. This suggests that overall gains in DALYs from all NTD programmes would be substantially greater than the 600 million DALY figure. The stated commitments of donors should be translated into resources to redress the inequities of financing, from which NTD programmes presently suffer, to give the poor what they deserve: access to free, high quality effective products as they continue to be exposed to an avoidable chronic pandemic which claimed at least ten-times more lives than the Ebola epidemic in a single year.

Contributors
DHM wrote the first draft and took the lead role in development of the paper; LS and DE contributed to further development of the content and structure of the paper, in particular the policy elements and editing, and agreed to the final version.

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