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DFID Support to the Control of Neglected Tropical Diseases: The Context

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Review and Recommendations

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ABBREVIATIONS

ALB	Albendazole
API	Active Pharmaceutical Ingredient
APOC	African Programme for Onchocerciasis Control
BMGF	Bill and Melinda Gates Foundation
CDTI	Community-Directed Treatment with Ivermectin
BT	Blinding Trachoma
CFGM	Complementary Feeding and Growth Monitoring
CHOICE	Choosing Interventions that are Cost Effective
CM	Case Management for Childhood Pneumonia
CNS	Central Nervous System
DALY	Disability Adjusted Life Years
DCP	Disease Control Priorities
DEC	Diethylcarbamazine
DOTS	Directly Observed Therapy
FGS	Female Genital Schistosomiasis
GAELF	Global Alliance to Eliminate Lymphatic Filariasis
GHP	Global Health Partnership
GNNTD	Global Network for Neglected Tropical Diseases
GSK	Glaxo Smith Kline
GWD	Guinea Worm Disease
HAART	Highly Active Anti Retroviral Therapy
IFF	International Financing Facility
IVM	Ivermectin
J&J	Johnson & Johnson
LEV	Levamisole
LF	Lymphatic Filariasis
LFSC	Lymphatic Filariasis Support Centre
LSTM	Liverpool School of Tropical Medicine
MBD	Mebendazole
MDA	Mass drug administration
MDG	Millennium Development Goal
NEJM	New England Journal of Medicine
NTD	Neglected Tropical Disease
ONCHO	Onchocerciasis
ORT	Oral Rehydration Therapy
PC	Preventive Chemotherapy
PYR	Pyrantel
PZQ	Praziquantel
RTI	Research Triangle Institute
SAFE	Surgery, antibiotics, facial cleanliness, environmental hygiene
SCH	Schistosomiasis
SCI	Schistosomiasis Control Initiative
STH	Soil-Transmitted Helminthiasis
TCC	The Carter Center
TRA	Trachoma
USAID	United States Agency for International Development
WHA	World Health Assembly

1 INTRODUCTION

Neglected tropical diseases (NTDs) is the term used for a number of different parasitic and bacterial infections. It includes lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), schistosomiasis (Bilharzia), leishmaniasis (kala-azar), dracunculiasis (guinea worm), trypanosomiasis (sleeping sickness) and soil transmitted helminthiasis (STH).

NTDs tend to receive little attention because they have a low case mortality rate (despite the fact that mortality is high given the large numbers infected and that they are responsible for high levels of morbidity). Hotez et al report that the burden attributed to NTDs exceeds that of TB and malaria and is roughly two thirds that of HIV/AIDS¹. In addition, their impact is often underestimated as many of the effects e.g. anaemia, diarrhoea, are attributed to other causes. Nevertheless, control of NTDs represents some of the best buys in international public health in terms of costs per disability adjusted life year (DALY) averted. In some cases growth and physical defects can be reversed by treatment for helminthiasis. The poor, and other marginalised groups, suffer disproportionately and although significant progress is being made many trends pose particular challenges e.g. climate change, greater urbanisation and migration. Reduction in the health burden related to NTDs should accelerate progress towards MDG 1 (improved nutrition), MDGs 2 and 3 (increased likelihood for school attendance especially for girls who are often more adversely affected by NTDs), as well as the health related MDGs (4, 5 and 6).

The UK plans to make a substantial commitment to support efforts to control NTDs. Two consultants David Crompton and Mark Pearson were commissioned to advise DFID on how its support might be best utilised. ToRs are attached at **annex 1**. As part of this work the team liaised closely with DFID staff, reviewed the literature and consulted with technical experts and partners working in this field. This included those working in Governments, in bilateral and multilateral donor organisations, pharmaceutical companies and global partnerships. A full list of those consulted is at **annex 2**.

The NTDs are now much less neglected. The US Government recently expanded its existing NTD programme, committing \$350m to combat the 5 “able to treat” conditions over the next 5 years. Strongly supportive statements have also been made by the G8, the EC and the Director General of WHO (see box 1).

¹ Hotez PJ et al 2007 Control of Neglected Tropical Diseases, NEJM Vol 357 pp1018-1027
DFID Health Resource Centre

Box 1: Key Policy Statements

2008 US/EU Summit Declaration, Ljubljana, Slovenia 10th June 2008

“We, the leaders of the United States of America and the European Union, met today We share a strong interest in supporting global health. We will join together to combat **neglected tropical diseases**. ”

US President George W Bush, Washington DC, 2nd July 2008

“We should set a goal to **treat** at least 75% of the people with **neglected tropical diseases** in the most affected countries.”

[The President had already announced a new global initiative making a total of \$350 million available over five years to provide integrated treatment of more than 300 million people in Africa, Asia and Latin America – for **neglected tropical diseases**; LF, ONCHO, SCH, STH and TRA.]

G8 Meeting, Hokkaido, Toyako, Japan, 9th July 2008

“We met at to address key challenges we face today. We welcomed substantial progress on our previous commitments to fight HIV/AIDS, tuberculosis, malaria and polio and **agreed to support the control or elimination of neglected tropical diseases** to reach at least 75% of people with NTDs. ”

Recommendation from the G8 Health Experts Group, 8th July 2008

25. Efforts to control or eliminate NTDS need to be invigorated. The G8 will work to support the control or elimination of diseases listed by the WHO through such measures as research, diagnostics and **treatment**, prevention, awareness-raising and enhancing access to safe water and sanitation. promoting adequate **integrated public health approaches, including through the mass administration of drugs**, we will be able to reach at least 75% of the people affected by certain **major neglected tropical diseases** in the most affected countries in Africa, Asia and Latin America bearing in mind the WHO plan. With sustained action for 3 – 5 years, this would enable a very significant reduction of the current burden with the elimination of some of these diseases.”

WHO Director-General Dr Chan at the World Health Assembly, 19th May 2008

I have mentioned at least one “perfect storm” brewing on the horizon. I believe that control of **neglected tropical disease** represents the opposite: a “perfect rainbow”. We now see a whole spectrum of opportunities that have converged in a most harmonious way. Safe and powerful drugs are being donated or made available at very low cost. Integrated approaches have been devised for tackling several diseases at once. A strategy of mass preventive chemotherapy, aimed at reaching all at risk, rivals the protective power of immunization. As you know, we are on the brink of eradicating guinea-worm disease”

Although there is potential to eliminate some of the diseases there is often considerable uncertainty as to how to do this and how rapidly it can be achieved. The need to sustain high levels of coverage in difficult settings pose major challenges. In some cases effective tools are available, in others current tools are inadequate. This report, and the DFID support, focuses on the former.

2 CURRENT STATUS OF NTDS

2.1 Overview

Table 1 below presents current understanding on the causes, impact and plans for eliminating or eradicating¹ the condition in question. Kalazar and sleeping sickness are not covered further as existing tools need to be improved.

Disease	Dracunculiasis/ Guinea worm disease (DRAC)	Lymphatic filariasis/ elephantiasis (LF)	Onchocerciasis/ river blindness (ONCHO)	Schistosomiasis/ Bilharzia (SCH)	Soil-transmitted helminthiasis (STH)	Trachoma/Blinding trachoma (BT)
Causative agent(s)	<i>Dracunculus medinensis</i> (nematode)	<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> , <i>B. timori</i> (nematodes)	<i>Onchocerca volvulus</i> (nematode)	Mainly <i>Schistosoma haematobium</i> (urinary) and <i>S. mansoni</i> (intestinal) - <i>S. japonicum</i> and <i>S. mekongi</i> to a lesser extent (trematodes)	<i>Ancylostoma duodenale</i> and <i>Necator americanus</i> (hookworms), <i>Ascaris lumbricoides</i> (roundworm), <i>Trichuris trichiura</i> (whipworm) – (nematodes)	<i>Chlamydia trachomatis</i> (Gram negative micro-organism)
Vector/ intermediate host	Freshwater copepods contaminating drinking water; transmission is seasonal leading to annual reinfection of people.	Mosquitoes (breed in fresh and stagnant water)	Blackflies (breed in running fresh water)	Freshwater snails – leads to focal endemicity in countries	None known	None known (house flies as mechanical vectors)

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No. countries with endemicity	9 at end of 2007.	81 (transmission may have stopped in 4 of these)	28	53	122	
No. people at risk of infection (groups affected)	NA. (all ages)	1.2 billion (adolescents and adults)	100 million (adults)	200 million, 70 million with <i>S.haematobium</i> and 130 million with <i>S.mansoni</i> (school ages children, women of reproductive age)	1.3 billion, of which 740 million are children (often >2 infections per person) (school ages children, women of reproductive age (hookworm only)	300 million (children and adults – especially women)
No. people with morbidity	9585 at end of 2007 (5815 in Sudan, 3358 in Ghana, 313 in Mali, 73 in Nigeria, 26 in remaining 5 countries).	120 million (mainly adults; men>women)	37 million	Probably all infected individuals	>300 million children; others with “subtle” morbidity	40 million
DALY value (‘000)	Not yet available, but probably now small.	5777	484	1702	2882	2329

Disease	Dracunculiasis/ Guinea worm disease (DRAC)	Lymphatic filariasis/ elephantiasis (LF)	Onchocerciasis/ river blindness (ONCHO)	Schistosomiasis/ Bilharzia (SCH)	Soil-transmitted helminthiasis (STH)	Trachoma/Blinding trachoma (BT)
Manifestations	Blister formation, itching, intense pain, bacterial invasion leading to ulcers and abscesses, permanent impairment of joints and reduced mobility; seasonality renders people bedfast around harvest time, worker output is reduced and school attendance affected. Other health care affected; e.g. children not taken for immunization.	Impaired lymphatic system, bacterial invasion, pain and fever, adenolymphangitis, gross pathology of limbs (hence elephantiasis), breasts and genitalia, social stigma, loss of productivity.	Skin lesions leading to severe itching (sleep deprivation) and depigmentation; eye lesions from conjunctivitis, visual impairment and blindness. Loss of productivity as agricultural land is abandoned.	Bleeding, liver fibrosis, kidney damage, bladder cancer, female genital lesions accelerating HIV infection; pathology is irreversible; "subtle" morbidity.	Mainly children – abdominal pain, nausea, reduced food intake, impaired growth, diminished iron status and anaemia, poor educational performance, school absenteeism: biliary and intestinal obstruction sometimes fatal. Effects on iron status affect maternal health and pregnancy outcomes.	Conjunctivitis with inflammation and scarring, entropion (deviated eye lashes touching the eyeball), corneal opacity, irreversible blindness.

Disease	Dracunculiasis/ Guinea worm disease (DRAC)	Lymphatic filariasis/ elephantiasis (LF)	Onchocerciasis/ river blindness (ONCHO)	Schistosomiasis/ Bilharzia (SCH)	Soil-transmitted helminthiasis (STH)	Trachoma/Blinding trachoma (BT)
Public health intervention	Protect people from contact with open water sources, management of water supply to prevent contamination with worm larvae, filtration of water to remove infected copepods and water treatment with ABATE® to kill copepods.	IVM+ALB or DEC+ALB Vector control and improved water and sanitation	MDA with IVM Vector control and improved water and sanitation	MDA with PZQ Vector control and improved water and sanitation	MDA with ALB or MBD (LEV and PYR in reserve) Vector control and improved water and sanitation	SAFE strategy (surgery, antibiotics, facial cleanliness, environmental hygiene) including MDA with azithromycin, the A (antibiotic) element. Vector control and improved water and sanitation
Weakness of Current Approaches	Limited access to public health control measures in Ghana in Sudan	Limited access to essential medicines	Limited access to essential medicines	Limited access to essential medicines	Limited access to essential medicines	Limited access to essential medicines

Disease	Dracunculiasis/ Guinea worm disease (DRAC)	Lymphatic filariasis/ elephantiasis (LF)	Onchocerciasis/ river blindness (ONCHO)	Schistosomiasis/ Bilharzia (SCH)	Soil-transmitted helminthiasis (STH)	Trachoma/Blinding trachoma (BT)
Elimination/ eradication status	WHA 57.9 - to complete eradication of dracunculiasis by 2009. Elimination probably achievable by then if increased support provided; certification of eradication predicted for 2015 provided that interventions can be applied without disruption.	WHA 50.29 – to eliminate lymphatic filariasis as a public health problem. Elimination probably achievable in smaller countries.	WHA 47.32 – to control onchocerciasis through distribution of ivermectin. Excellent response, with progress in reducing public health significance of the disease in West Africa (WHO, 2002a).	WHA 54.19 – to reach at least 75% of school-age children with anthelmintic treatment by 2010. Achievable in some countries if sufficient PZQ obtained. No prospect of elimination without universal access to safe water supply and effective sanitation.	WHA 54.19 - to reach at least 75% of school-age children with anthelmintic treatment by 2010. Achieved in a few countries e.g. Burkina Faso and Cambodia. No prospect of elimination without universal access to safe water supply and effective sanitation.	WHA 51.11 – global elimination of blinding trachoma by 2020 as a public health problem. Possible in some areas given support and resources to apply the SAFE strategy.

ⁱ **Definitions** (Certification is the responsibility of the World Health Organization: see WHO, 2002b)

Elimination. A reduction to zero of the number of new cases of a specific infection in a defined geographical area, as a result of deliberate efforts. Continued intervention or surveillance measures are required.

Eradication. A permanent reduction to zero of the world-wide prevalence of infection caused by a specific agent, as a result of deliberate efforts. Continued measures are no longer required.

2.2 Key Stakeholders in NTD Control

An overview of the stakeholders and their main responsibilities is outlined in the table below.

Table 2: Key Stakeholders in NTD Control

Type of Partner	Key Partner	Key Roles
Governments	Governments	Development of integrated national plans, implementation, funding
Lead partners	WHO (UNICEF, WFP, FAO)	Strategic direction, technical assistance, capacity building, procurement of essential drugs, monitoring and evaluation, support for surveillance, resource mobilisation, donor coordination, advocacy
	Global Network for Neglected Tropical Diseases (GNNTDC)	Advocacy and resource mobilisation
	Technical agencies and academia (CDC, IMT, LSTM)	Research and knowledge, training and evaluation
Donors and technical partners	Donor agencies (USAID)	Funding (grants and soft loans), advocacy and technical expertise
	Foundations (BMGF)	Funding (grants), advocacy and technical expertise
	Pharmaceutical manufacturers	Sustainable supplies, donations, pharmacovigilance, logistics and research
Disease based initiatives	APOC, GAELF, RTI, SCI, Carter Centre, others	Assist national programmes in implementing NTD control. Co-ordination, consensus building and resource mobilisation.
Non Government sector	Many	Advocacy, financing, technical and operational support, implementation

Adapted from WHO 2008

2.3 The Importance of Integrated Approaches

There is growing consensus that integrating various NTD programmes - as well as integrating treatment - is both feasible and beneficial (see boxes). APOC, for example, is increasingly looking to integrate its efforts with other programmes in countries where onchocerciasis is a public health problem. In 2006, the WHO shifted its strategy away from disease specific interventions to helping the “maximum number of people at risk who could be treated with a set of drugs”.

Box 2

More integrated approaches to neglected diseases

There seems growing consensus that a more integrated approach to tackling at least some of the neglected diseases would be both feasible and beneficial. Where opportunities arise, integration of technical strategies could include the combined delivery of interventions or joint activities at the levels of mapping, training, procurement of drugs and equipment, and surveillance and monitoring². A study in Uganda in mid-2003³ noted that discussions were underway between the

² Draft note of issues and recommendations for intensified control, from the International Workshop on Intensified Control of Neglected Diseases, Berlin 10-12 December 2003.

³ Caines K., et al 2003., Impact of Public-Private Partnerships Addressing Access to Pharmaceuticals in Low Income Countries: Uganda Pilot Study, Initiative on Public-Private Partnerships for Health, Switzerland, 2003. ISBN: 2-94 0286-10-8.

National Onchocerciasis Control Programme, the Programme to Eliminate LF and the Schistosomiasis Control Initiative on how best to integrate activities such as training, supervision, advocacy, registration and drug distribution. Integrated community-directed treatment for onchocerciasis, schistosomiasis and intestinal helminths was planned in 6 districts, with potential for considerable benefit and increased efficiency. The benefits of integrated activities can be particularly great for control programmes that rely on logistically demanding strategies, such as mass drug administration. WHO has proposed consolidation of the various components of control for several neglected diseases into a single matrix. This would enable health administrations and district health managers to identify opportunities for shared activities, eliminate redundancies, and thus deliver services with greater efficiency and broader impact on the total burden of disease. Developments of this kind will require much closer collaboration between individual GHPs for neglected diseases at global as well as country levels. This collaboration should cover advocacy for a group of diseases rather than an individual disease, as well as support for delivery of technical strategies. Source: Gaines 2004

Four extremely prevalent NTDs (lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis) are amenable to integrated preventive chemotherapy (PC), a safety tested, well tried, public health intervention that successfully reduces and controls morbidity. It is integrated in the sense that more than one drug can be given at once to the same person to treat more than one NTD. Preventive chemotherapy can also be used against trachoma, but not as part of the integrated strategy⁴.

Box 3: Impact of Preventive Chemotherapy

The devastating toll of a subset of NTDs⁵ can be dramatically reduced with mass drug administration (MDA) using a combination of medicines from a group of highly effective medicines. Each medicine has an excellent safety record that has accrued from the use of millions of doses. WHO recommends the strategy of Preventive Chemotherapy which targets a group of NTDs and at risk-populations rather than specific diseases or infected individuals as NTDs tend to occur together in the same geographic cluster. Preventive Chemotherapy, even when deployed without other complementary interventions such as improved hygiene and sanitation, surgery, vector control and health promotion, can lead to a significant reduction of morbidity and transmission of helminthic diseases and blinding trachoma. A precondition for success is uninterrupted access to good quality, low cost medicines in order to reach high coverage of populations at risk. WHO 2008a

The chronic ill health that characterises the four forms of helminthiasis has been demonstrated to be relieved by regular treatment with WHO-recommended oral drugs (WHO, 2004) given once or twice yearly in tablet form according to PC guidelines (WHO, 2006). In some cases, transmission rates can be reduced. For example, the drug regimen for lymphatic filariasis kills the microfilariae that must be ingested by the vector mosquitoes that sustain and transmit the infection (Ottesen *et al.* 1997). Regular treatment of primary school-age children for soil-transmitted helminthiasis was judged to be the most cost effective public health measure for a low income country to undertake according to a World Bank review (World Bank 1993).⁶

Preventive chemotherapy also lends itself to integration with other public health measures (see box 3 below). There is little systematic evidence on the financial benefits associated with integration⁷.

⁴ The same is true of Visceral Leishmaniasis (kala-azar) requires diagnosis followed by treatment with pentavalent antimony compounds. Dosage and adjustment of treatment need to be made according to patient clinical response. Bone marrow biopsies may be required – none of this lends itself to MDAs or community interventions (see WHO, 2004).

⁵ Lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma

⁶ NB: A review by the Cochrane commission did not come to the same conclusion.

⁷ Plag 1995 estimated that in Indonesia programme costs could be reduced by 35% by integrating leprosy activities into TB programmes. This suggests that some cost savings might be possible. It is not clear how widely relevant such findings are

2.4 Cost Effectiveness of Available Interventions

Interventions aimed at NTDs are more cost effective than most interventions and orders of magnitude more cost effective than many of the health interventions currently funded by the donor community. The following table presents data from the Disease Control Priorities programme and suggests that almost all interventions considered cost less than \$100 per DALY. The example of dengue, however, shows that NTD control may not always be cost effective. (A useful rule of thumb is that an approach is cost effective if it cost less than 3 times per capita income).

Table 3 Cost Effectiveness of Different NTD Interventions

Disease	Intervention	Cost per DALY ⁸ averted
Lymphatic filariasis	In areas of high prevalence, annual mass drug administration to treat the entire population at risk for a period long enough to interrupt transmission and achieve elimination (or control for a 30 year period)	\$4 - \$8 (\$29)
	DEC-fortified salt	\$1-\$46
	Vector Control	\$48-\$303
Schistosomiasis	Treatment with albendazole	\$3-\$7
	Combined albendazole and praziquantel	\$8-\$19
Trachoma	Surgery to repair eyelids	\$4 - \$82
Onchocerciasis	Community-directed ivermectin treatment programmes with drugs provided free of charge	\$6
Soil-transmitted helminthiasis (hookworm, roundworm and whipworm)	Mass school-based treatment using albendazole	\$3
Leprosy	Case detection and treatment	\$38
	Prevention of disability	\$1-\$110
Dengue	Case management	\$587
	Immunisation	\$3040
Leishmaniasis	Case finding and treatment	\$18
African Trypanosomiasis	Case finding and treatment: melarsopol eflornithine	<\$10 <\$20

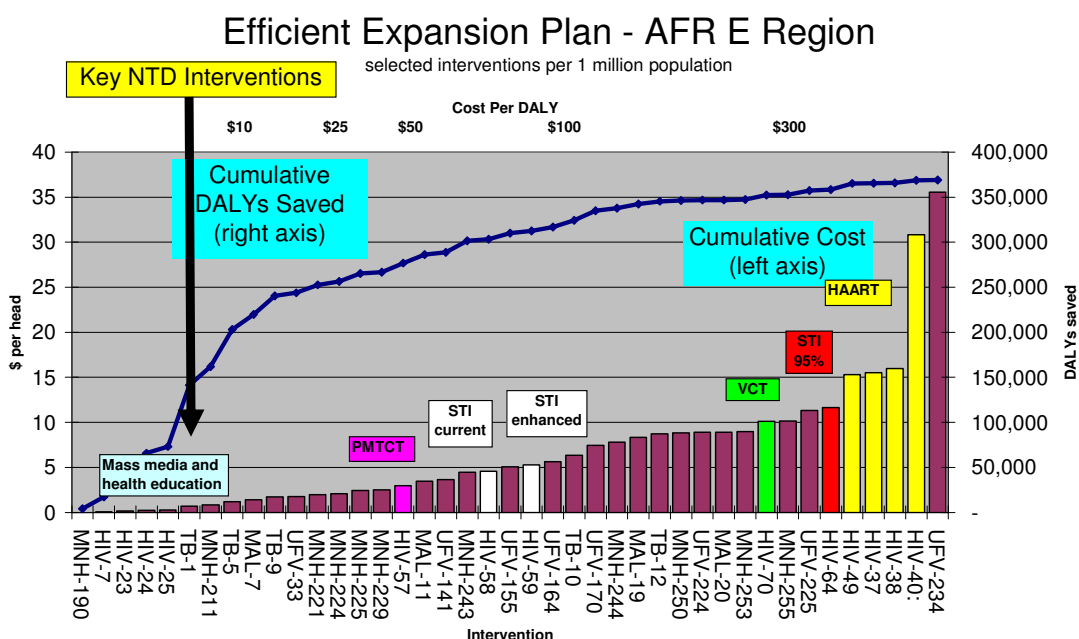
Modelling of the impact of LF interventions suggests that the cost per DALY for elimination in 6 years at \$4.4 rising to \$8.1 if it takes 10 years. This compares to control of LF through MDA for 30 years at \$29 per DALY. The use of DEC fortified salt is far more cost effective (\$1 to \$3 per DALY where transmission is interrupted in 4 years or less and up to \$46 when transmission continues but at low levels) but compliance is difficult to ensure⁹. Vector control is much less cost effective but still reasonably so when it leads to elimination. (DCP 2006)

⁸ The DALY is a measure of the burden of ill health taking into account reduced life expectancy and quality of life. The number of DALYs lost as a result of a disease is calculated by estimating the number of years lost due to premature death plus equivalent years of ill health.

⁹ Salt fortified with DEC has been used in various places in Asia (GPELF, 2005) and appears to eliminate *Wuchereria bancrofti* after 6 months at a concentration of 0.1% when added to salt. There are problems with community compliance, logistics of distribution, production supply and so on. GPELF (Global Programme for the Elimination of Lymphatic Filariasis) 2005. Annual Report on Lymphatic Filariasis 2003. Geneva: World Health Organization.

The following figure compares the cost effectiveness of NTDs with interventions with other diseases. It is based on data from the WHO CHOICE¹⁰ model and sets out what would be the most efficient use of resources (or efficient expansion plan) in AFR E¹¹ region. It shows how much each intervention aimed at for 5 diseases (HIV/AIDS, malaria, TB, childhood diseases, maternal and neonatal health) would buy in terms of improved health (in DALYS) and at what cost (in \$ per head). Also included at the top of the chart is an indication of the cost per DALY achieved by the different interventions (the most cost effective being on the left hand side).

Figure 1



As we move from left to right we move from the most cost effective interventions (in this case community-based case management for neonatal pneumonia) to the least cost effective ones (in this case adding CFGM¹² to Vit. A Suppl., Zinc Suppl., ORT & Case management for childhood pneumonia - CM (@95%) + Measles vaccination (@95%). This is reflected in the fact that as the total expenditure increases the *additional* health gains tend to decline. Spending \$5 per head saves 300,000 DALYs per 1 million population, spending \$10 per head saves around 350,000 DALYs whilst spending \$35 per head (with most of the increase accounted for by moving from simple HAART with DOTS to HAART plus with DOTS) adds very little more in terms of benefits. In practice, all NTD interventions would be amongst the most cost effective interventions – in most cases cost is below \$25 per DALY. As the figure shows this would place them at the far left hand side of the chart and amongst the most cost effective interventions.

2.4 Economic and Fiscal Benefits

Beyond the immediate health benefits reduced ill health due to NTDs can also have broader (and potentially very large) economic and fiscal benefits. For example, Ramaiah et al (2000) estimate that preventing one case of chronic LF disease (costing just over \$8) saves over 58 working days

¹⁰ The CHOICE model uses regional estimates of costs and the strength of evidence on effectiveness is variable

¹¹ Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania Zambia, Zimbabwe

¹² Improved complementary feeding through nutrition counselling and providing nutrient dense food for all underweight children 6-12 months old identified through growth monitoring and promotion (CFGM)

which, if not substituted for by others, would generate additional earnings of around \$39¹³ and averts treatment costs of almost \$1.5. Ramu et al (1996) found that uninfected people were 27% more productive than people infected with chronic LF in case control studies in India.

2.5 Social Costs

Lymphatic filariasis is estimated by WHO to be the second largest cause of disability in the world. Victims are often subject to severe societal discrimination resulting in poor educational, employment and marriage prospects. The poor are more likely to be affected by NTDs and face more serious consequences. Brooker et al (2004) found that children, women of reproductive age and pregnant women were far more likely to suffer from hookworm anaemia because of their poor underlying iron status. According to the DCP helminths are “intimately associated with poverty, poor sanitation and the lack of clean water”. de Silva et al (2003) demonstrate the negative correlation between income level and helminths infection. Having said this there have been no benefit incidence studies to assess the extent to which the poor benefit from public subsidies. Nonetheless, it would be reasonable to conclude that efforts to address NTDs are likely to be focused on the poor and vulnerable.

¹³ which, in itself, highlights the fact that those who suffer are amongst the poorest and lowest earners

3 POSSIBLE INTERVENTIONS

This section identifies a number of areas where support may be needed. It is not intended to be fully comprehensive but reflects the views and priorities put forward by the key informants.

3.1 Supporting the Eradication of Dracunculiasis/Guinea worm disease

There is a real prospect for the elimination and ultimate eradication of guinea worm disease (GWD) in line with WHA 57.9. The number of cases of the disease has fallen from 3.5 million in 1986 to 9,585 in 2007. This achievement has been achieved through the efforts of the governments of endemic countries with support from the Carter Center (TCC), WHO, UNICEF and many partners. TCC supports interventions to disrupt transmission; UNICEF supports the provision of safe water supplies; WHO supports surveillance following elimination and accepts responsibility for certification.

The estimated cost of reaching the point of declaring that guinea worm disease has been eradicated is estimated at \$88m. The Bill & Melinda Gates Foundation (BMGF) is, we understand, about to commit \$40m to accelerate the elimination/eradication process. This is likely take the form of a challenge fund – requiring matching support from other donors. There is, therefore, a shortfall of some \$48 million from 2010 onwards. The figures are shown in table 4 below.

Table 4. Estimated Costs of Elimination/Eradication of Guinea Worm

\$m	2008	2009	2010	2011	2012	2013	2014	2015	Total
Carter Center	1.5	10.5	12.5	9.5	7.5	4	2	0.5	48
WHO	7.5	6.5	6	6	5	3.5	3	2.5	40
Total	9	17	18.5	15.5	12.5	7.5	5	3	88
Cumulative	9	26	44.5	60	72.5	80	85	88	
Funding pledged by BMGF	32	2	2	2	2				40
Outstanding Funding gap \$			8.5	13.5	10.5	7.5	5	3	48
Outstanding Funding gap £	0	0	5.3	8.4	6.6	4.7	3.1	1.6	30

Source: WHO/NTD, August 2008 using £1 = \$1.6

A more detailed table of the financing gaps and the proposed timetable for eradication is provided at annex 3. At the present rate of progress hardly any areas are likely to be reporting cases of disease by the end of 2010. Then will begin the tedious, but most important task, of routine surveillance for a sufficient time to permit certification of eradication (timeline is in **annex 3**). This will be organized and managed by WHO.

3.2 Addressing Schistosomiasis and Lymphatic Filariasis

These conditions were prioritised given their health impact, the availability of cost effective interventions, the fact that they lend themselves to integrated preventive chemotherapy and outstanding financing needs

3.2.1 Treatment of Schistosomiasis with Praziquantel

Many studies demonstrate that annual treatment with a single oral dose (40-60mg/kg, WHO, 2004) provides relief from either of the common species of schistosome has the major benefits for patients (Richter, 2003; see chapter 10 in Crompton & Savioli, 2006). (Differences in morbidity relate to *haematobium's* location in blood vessels of the urinogenital tract and *mansoni's* in the blood vessels of the hepatic portal system).

Evidence of impact is summarised in Reich (1998). In more specific terms access to PZQ has the following benefits:

Schistosoma haematobium ; 70 million people in Africa with morbidity (van der Werf *et al.* 2003)

1. **Significant reductions** will occur in prevalence and intensity of infection in individuals and in the community (King *et al.* 1988, 1990).
2. **Marked reversal in morbidity** will follow including haematuria, dysuria, female genital pathology, bladder wall pathology, bladder cancer and hydronephrosis. Blood loss contributes to reduced iron status and anaemia (Richter, 2003). In long standing infections in people >40 years residual pathology may remain but is significantly reduced after oral PZQ.
3. **Bladder cancer**, resulting from a causal relationship with infection, will decline. Sixteen percent of bladder cancer cases in Egypt attributed to *S.haematobium* (Bedwani *et al.* 1998). *Schistosoma haematobium* has been designated as having carcinogenic properties (IARC, 1994).
4. **Increased growth and physical fitness** will be seen in children and better working capacity in adults (see Richter, 2003).
5. **Female genital schistosomiasis** will decline reducing risks of contracting HIV infection (Poggensee & Feldmeier, 2001), Suffers were found to be three times more likely to contract HIV in Zimbabwe (Kjetland *et al.* 2006). There are conjugal benefits following treatment (Richter, 2003).
6. **Predicted reduction in death rate** currently estimated at 150,000 annually due chiefly to kidney failure (van der Werf *et al.* 2003).
7. **Partial increase in immunity** to further infections following a single dose of PZQ (Mutapi *et al.* 1998).

Schistosoma mansoni; 130 million people in Africa with morbidity (van der Werf *et al.* 2003)

1. **Significant reductions** will occur in the prevalence and intensity of infections in individuals and in the community (Olsen *et al.* 2000).
2. **Marked reversal in morbidity** will follow including bloody stools, hypertension, periportal fibrosis, hepatomegaly (occurs in most individuals before treatment) and splenomegaly (Richter, 2003).
3. **Increased physical fitness, nutritional status and food intake** will be seen in children and better working capacity in adults (see Richter, 2003).

There are also numerous, less common, but equally serious problems including CNS involvement, colitis, appendicitis, retarded intrauterine growth and prostatic fibrosis.

Regardless of the species, more men and boys appear to be affected than women and girls, but **women and girls are more adversely affected** because of blood loss. The issue of Female Genital Schistosomiasis (FGS) due to *S.haematobium* is now being increasingly recognized. Offering treatment to women requires sensitivity to cultural nuances and the possibility of pregnancy.

The lack of funding for drugs and uncertainties over future availability were seen as the key constraint to progress. The capacity at the country level to deliver programmes effectively was seen as a major concern though most respondents felt that the emphasis should be on the former and that many countries have demonstrated an ability to secure funds for implementation once drugs are available. The case for focusing on purchasing non donated drugs is looked at further below.

3.2.2 *Treatment of LF with Diethylcarbamazine*

DEC, one of the two drugs of choice for LF, is the cheapest of the anthelmintic drugs used for integrated preventive chemotherapy. Provision of more DEC will reduce morbidity and social marginalization, and will contribute to the process of stopping transmission. However, DEC cannot be used in places where onchocerciasis occurs concurrently with LF. As a result DEC is restricted to LF endemic areas in Asia (WHO 2004). More DEC would make a major contribution to the attainment of WHA 50.29. There is no evidence of loss of efficacy of DEC when used in public health interventions.

3.2.3 *The Case for Purchasing Non-donated Drugs in Support of Preventive Chemotherapy: Praziquantel (PZQ) and Diethylcarbamazine (DEC)*

Access to drugs is a key constraint (see box 2 earlier). This was confirmed in discussions with key stakeholders. Despite their low cost and cost effectiveness, and the availability of drug donations by the pharmaceutical companies, there is an outstanding demand for a range of safe and highly effective products.

A coordinated plan for the procurement of essential drugs for integrated PC has been developed by WHO's Department of Control of Neglected Tropical Diseases (WHO/NTD) (WHO 2008a). This forms part of a facility support all aspects of drug procurement¹⁴.

This plan forms part of broader efforts which bring together the key actors (health authorities in endemic countries, funding agencies, pharmaceutical companies, and WHO) which aims to progress:

- mobilizing resources to procure adequate quantities of good quality medicines to be deployed free of charge in endemic countries to reach 100% coverage by 2013;
- ensuring adequate supply of NTD medicines;
- implementing a simple information system to track progress and provide a sound basis for estimating medicine needs.

Currently drugs for PC are obtained through donations by pharmaceutical companies, pooled procurement by UNICEF, WHO, and implementing agencies, loans from the World Bank, government budgets, bilateral agencies, philanthropic donors and NGOs. Table 5 below provides details of donated medicines (and direct procurement of DEC). For more details on donations see **annex 4**.

¹⁴ Forecasting of needs, prequalification of suppliers, procurement of non-donated drugs, coordination of application processes, shipping etc."

Table 5. Medicines provided by donation (2009 – 2013) and direct procurement (of DEC)

Medicine	Total number of tablets	Share of global need	Sources
ALB	3,393 million	49%	Donation by GSK
MBD	250 million		Donation by J&J as substitute of ALB for STH
DEC	4,562 million	63%	Direct procurement by Brazil, India and Thailand
PZQ	100 million	5%	Donation by Merck KGaA
IVM	1,967 million	100%	Donation by Merck & Co Inc

Source WHO 2008a

It should be noted that Table 5 provides details of PZQ donation only. If existing donor commitments to purchase PZQ are included in the figures above, then the share of global need already covered under existing purchase and donation commitments would be greater than the 5% indicated. Although exact donor commitments for PZQ purchase have not yet been obtained, indications are that existing commitments fall far short of the finance needed to purchase the 400 million tablets required annually, based on health need. Thus, a major financial contribution to this requirement now will bring major public and individual health benefit.

WHO estimates that to scale up coverage of PC rapidly (from around 30% coverage in 2009 to 100% coverage by 2013 – **annex 5**) and make a major impact in reducing the disease burden due to its target NTDs will require some \$260m during the period 2009 – 2013. Of this sum, \$222m is for drugs and \$38m (15% of total) is for associated costs (see footnote 13).

Table 6. Funding shortfall for cost of tablets needed during 2009-2013¹⁵

Medicine	2009	2010	2011	2012	2013	Total
ALB	\$8 million	\$12 million	\$16 million	\$12 million	\$16 million	\$64 million
DEC ¹⁶	\$1 million	\$2 million	\$3 million	\$3 million	\$2 million	\$11 million
PZQ	\$12 million	\$21 million	\$33 million	\$37 million,	\$44 million	\$147million
IVM	-	-	-	-	-	-

Source WHO 2008a

¹⁵ These costs exclude other expenditures that would need to be undertaken by the procurement agency.

- Transport, insurance and custom clearance from the place of manufacture to the port of entry.
- Quality control of procure drugs.
- Technical assistance (if requested by governments of endemic countries) in planning programmes, monitoring and reporting.
- Co-ordination of logistics.
- Prequalification of suppliers by contracted specialists.

These would add around 15% to the total cost

¹⁶ Estimates of the need and cost of DEC to greatly increase coverage in Asia during the period 2009 to 2015 amount to \$27 million. This estimate will fall to \$11 million provided that India continues to purchase DEC for national programmes (as shown in the table).

As noted above, the PZQ funding shortfall is actually lower than indicated in Table 6 from the WHO Business Plan, due to the presence of existing donor finance commitments for purchasing PZQ. However, even if existing donor finance figures are included, there is still a large finance gap when compared with finance needed to supply total health need.

3.2.4 *Support for APOC*

APOC was established in 1995 in preparation for the ending of the Onchocerciasis Control Programme (OCP) in West Africa (WHO, 2002a). APOC's primary function is to continue the effort to eliminate and eradicate onchocerciasis. The intervention tool is the distribution of free ivermectin which is being donated for as long as necessary by Merck & Co Inc. The method of intervention is APOC's system of Community Directed Treatment with Ivermectin (CDTI). APOC relies on WHO sponsorship and funds from various donors. The monies are managed by the World Bank through its APOC Trust Fund. The UK's current contribution to the Trust Fund for a five-year period is about £0.5 million per annum. We understand that APOC has recently received a grant of £25 million from Merck & Co Inc..

APOC is making a major contribution to onchocerciasis control (see APOC, 2005). APOC's system of CDTI is highly regarded; the proven effectiveness of CDTI has made the strategy not only a model for the delivery of health interventions but also, increasingly, a vehicle for the concomitant distribution of multiple health interventions (see APOC, 2007). During the period 1996-2005, APOC's programme treated 40 million people with ivermectin in 16 endemic countries, and maintained a force of 261,000 workers for CDTI (see APOC, 2008).

According to its 2005 evaluation its main strategy CDTI "addresses an important neglected problem that affects mostly the rural poor; and it does so in a relatively low-cost manner". It is considered to have "a clear strategy, and has operationalised it through well-formulated objectives, plans and targets" and is "moving steadily towards its objectives, but still facing substantial challenges to continued satisfactory completion". It has also leveraged significant Government contributions, in the form of salaries of staff, facilities and equipment.

According to its Strategic Plan APOC needed some \$7m to cover phase II of its operations (to 2010) and a further \$46.4m to cover its phasing out period (to 2015) (For further details see **annex 6**). However, given recent pledges it is understood that this gap has now been filled.

3.2.5 *Support for the Lymphatic Filariasis Support Centre (LFSC)*

LFSC supports country programmes, gathers, collects and analyses data on progress and needs for the elimination programme and though its membership of the GNNTD is a strong advocate for NTD control. It also acts as the Secretariat for the Global Alliance to Eliminate Lymphatic Filariasis (GAELF). It receives financial support from DFID and from GSK for activities concerned with LF treatment and control. During the four-year period April 2004 to March 2008, DFID's financial support to LFSC amounted to £2.56 million of which around half is spent in endemic countries for LF control measures GSK intends to continue its financial support, currently of £100K annually, for the Centre's activities. Current DFID support of £0.5m per annum ends in March 2010.

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Information and evidence on which our report and its recommendations are based has been obtained from (1) reports, (2) published and electronic literature in the public domain, (3) circulated e-mail questions and (4) conference calls.

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ANNEX 1: TORS- NEGLECTED TROPICAL DISEASES

Background

NTDs is the term used for a number of different parasitic and bacterial infections. It includes lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), schistosomiasis (bilharzia), leishmaniasis (kala-azar), dracunculiasis (guinea worm), trypanosomiasis (sleeping sickness) and intestinal worms. Control of NTDs are some of the best buys in international public health in terms of costs per disability adjusted life year (DALY) averted

Collectively the NTDs cause half a million deaths annually. Though some of the NTDs have highly cost effective treatments for others there is a huge need for research to develop new tools. For example some parasitic infections can be quickly and cheaply controlled with as little as 25 pence per person a year whilst old and dangerous drugs are used to treat sleeping sickness; melarsoprol (an arsenic derivative) is so toxic that it kills 1 in 20 patients.

NTDs have often fallen outside sector planning processes. There are several global initiatives working on neglected tropical diseases. In recent years there have been real efforts at collaboration.

DFID supports two programs on NTDs. We have been a longstanding supporter of the onchocerciasis control and also support work on lymphatic filariasis. Each of these programs receive £0.5 million a year.

The UK is poised to make a large new commitment to NTDs in September 2008. This funding will be for those NTDs where we have existing tools available. At present most donor funds are channelled through public-private partnerships dealing with the individual diseases. These partnerships are now increasingly integrating their work. This work will contribute to international thinking on how best to impact on the control of neglected tropical diseases. New ones – longer term results – best to support these?

When the PM visited Washington in April 2008 the joint UK-US statement included a commitment to control of NTDs.

Extract from joint UK-US statement: “By putting in place this foundation for stronger health, we also build upon existing initiatives, including addressing the issue of neglected tropical diseases (NTDs). Approximately one billion people, mostly in the developing world, suffer from one or more NTDs. Building upon the President's announcement in February, the United Kingdom will support this effort to control or eliminate seven major NTDs. We will challenge other donors, including our G8 partners, foundations, and public, private, and voluntary organizations to meet the balance of this need to have a positive affect on the lives of hundreds of millions people in Africa, Asia, and Latin America.”

It has been estimated that \$1 billion over 5 years is needed to combat certain NTDs. In February 2008, President Bush announced \$350 million over 5 years for NTDs, as part of a call to donors to meet this gap. The Bill and Melinda Gates Foundation is the major donor on NTDs.

DFIDs new support will aim to increase coverage of interventions against NTDs. It should be done in a way that encourages government ownership.

Tasks

The consultants will:

Review the literature and consult with technical experts and partners on the disease burdens of the different NTDs and channel's of funding.

Incorporate the views of Ministries of Health in countries where NTDs are prevalent (phone calls with key respondents, from country case studies incorporated in other reviews)

Liaise closely with DFID staff.

The consultants will produce a report that answers the following questions:

- How new funding from donors can best be used to influence greater integration of NTDs specially at country level?
- Identify the pros and cons of different channels of funding so as to identify what would be the best route to channel new donor funds. Should new donor support be provided through individual disease programs or should it be provided through channels that integrate treatment of NTDs. What is the effectiveness and track record of channels currently being used by donors to provide funding for integrated NTD programs? The consultant/s should consider channels of funding for both the short term and the medium term.
- Identify the package of NTDs where there would be the greatest benefit from investment.
- Look at the evidence of funding need, particularly identifying areas where the gaps are greatest.
- Which would be the other donors best targeted for further support of NTDs?

A report of not more than 20 pages (not including annexes) will be produced. The report will be in two sections. The first section will be for wide circulation and contribute to wider donor thinking on NTDs. The second section will be specific recommendations to DFID

Timeline

The work needs to be done ASAP, over August and early September. Estimated total of up to 30 days. We estimate that 1-2 consultants will be needed.

ANNEX 2: LIST OF PERSONS CONSULTED

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L Brabin, Academic Unit of Obstetrics & Gynaecology, University of Manchester, UK

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ANNEX 3: FINANCING GAP AND TIMELINE GUINEA WORM ERADICATION

The Carter Center
Projected Funding Needed for Guinea Worm Eradication
Fiscal Years 2008-2015

Organization/Country	Transmission End Date	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	Total
The Carter Center (TCC) Costs										
Sudan	2012	\$6,809,924	\$5,690,687	\$4,471,094	\$3,498,958	\$2,586,243	\$1,373,331	\$827,630	\$0	\$25,057,865
Ghana	2011	1,940,219	1,524,151	1,203,351	996,689	781,414	121,293	76,930	0	6,623,948
Nigeria	2008	611,041	482,191	426,654	274,384	208,460	29,165	0	0	2,031,895
N. Sudan	2001	236,336	0	0	0	0	0	0	0	236,336
Mali	2009	611,374	543,869	478,924	337,842	251,622	141,556	86,285	0	2,451,501
Niger	2008	446,295	349,791	325,831	206,804	152,097	76,726	38,547	0	1,596,091
Ethiopia	2006	85,214	0	0	0	0	0	0	0	85,214
Global Initiative (GI)		2,987,207	4,802,939	3,502,291	2,825,064	2,152,921	1,391,302	696,049	0	18,357,774
GI Contingency		826,615	752,711	592,298	485,177	344,298	168,116	79,785	0	3,247,998
Headquarters		1,486,544	1,162,061	955,285	756,798	692,765	568,801	504,719	560,377	6,677,149
Direct Costs		\$16,019,768	\$15,328,401	\$11,955,729	\$9,381,812	\$7,149,818	\$3,880,119	\$2,109,944	\$560,377	\$66,365,770
Indirect Costs [⊖]		2,487,194	1,988,362	1,480,345	1,151,883	901,356	507,844	288,990	99,057	8,895,030
Total TCC Costs		\$18,486,962	\$17,316,763	\$13,446,074	\$10,533,495	\$8,051,174	\$4,387,963	\$2,398,934	\$659,434	\$75,260,800
Less: TCC Secured Funding		(18,700,000)	(8,917,000)	0	0	0	0	0	0	(22,717,000)
Total TCC Net Budget		\$1,786,962	\$11,299,763	\$13,446,074	\$10,533,495	\$8,051,174	\$4,387,963	\$2,398,934	\$659,434	\$52,543,800
WHO Costs, Net of Avail. Funding		7,453,438	5,546,333	5,125,390	4,895,305	4,314,689	3,295,637	2,503,646	2,331,320	35,454,758
Total Costs		\$9,240,400	\$16,845,096	\$18,571,464	\$15,418,800	\$12,365,863	\$7,663,600	\$4,902,580	\$2,990,754	\$87,998,558

⊖ Indirect costs fluctuate in this projected budget analysis. These fluctuating costs are the net result of available support for indirect costs from current grants and expected support for indirect costs from outstanding proposals, including a pending proposal to the Bill & Melinda Gates Foundation, which allows a maximum indirect cost rate of 15%.

Table 1 - Guinea Worm Eradication Campaign 2007-2015

Country	Year, # of Cases, Pre-Certification, Certification									
	2007	2008	2009	2010	2011	2012	2013	2014	2015	
Sudan	5,815	2,560	1,300	520	210	40	0-PC	ICT	CERT	
Ghana	3,358	1,380	525	210	40	0-PC		ICT	CERT	
Mali	313	125	30	0-PC			ICT	CERT		
Nigeria	73	35	0-PC				ICT	CERT		
Niger	11	5	0-PC				ICT	CERT		
Burkina Faso (2006)	0-PC			ICT	CERT					
Cote d'Ivoire (2006)	0-PC			ICT	CERT					
Togo (2006)	0-PC			ICT	CERT					
Ethiopia (2006)	0-PC				ICT	CERT				
Kenya (1994)					ICT	CERT				
Uganda (2003)					ICT	CERT				
Benin (2004)		ICT	CERT							
Mauritania (2004)		ICT	CERT							
Chad (1998)		ICT	CERT							
Total Cases	9,570*	4,105	1,855	730	250	40				
Projected % Reduction		-57%	-55%	-61%	-66%	-84%	-100%			

*Provisional. Excludes 15 cases exported from one country to another.

Key

	Transmission Ongoing (# of Cases)
	Transmission Interrupted – Pre Certification Stage Begins (PC), International Certification Teams Deployed (ICT)
	Certification of Eradication (CERT)

ANNEX 4: CURRENT STATUS OF DRUG DONATIONS

4.2.1 Disease	4.2.2 Drug (Donor)	4.2.3 Price
Onchocerciasis	Ivermectin (Merck)	Merck have committed to supply all that is needed.
Soil-Transmitted Helminths	Mebendazole (Johnson&Johnson) or Albendazole	J&J will donate approx. 100 million tablets of Mebendazole per year. Various suppliers of Albendazole at 1p/2¢ per tablet.
Trachoma	Azythromycin (Pfizer)	Donated to National Governments by Pfizer through the International Trachoma Initiative (ITI)
Lymphatic Filariasis	Ivermectin (Merck) + Albendazole (GlaxoSmithKline)	Merck and GSK combine to offer free treatment to over 200 million people at risk.
Schistosomiasis	Praziquantel (partial donation from E. Merck and MedPharm)	16 million tablets per year of Praziquantel are donated by MedPharm and 200 million tablets over the next 10 years by E. Merck. The remainder is purchased at 4p/8¢ per tablet.

Source: SCI

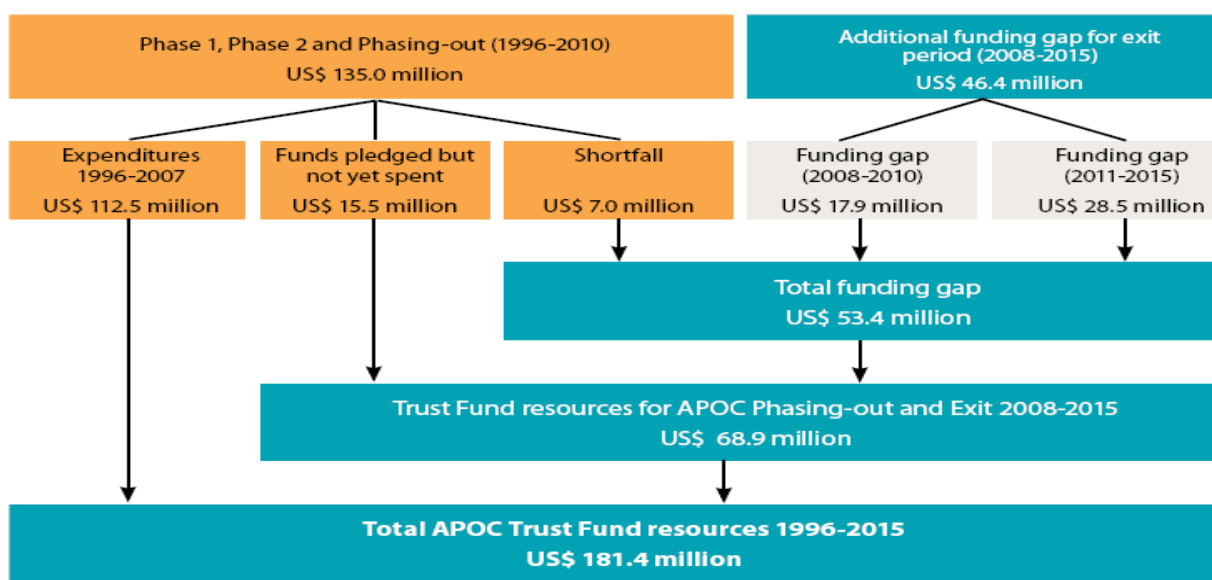
ANNEX 5: SCALE UP PATTERNS FOR STH AND SCH AT GLOBAL LEVEL

Year	Coverage rate for STH / SCH (Number of population treated/ Total number of target population)
2009	30%
2010	50%
2011	75%
2012	85%
2013	100%

ANNEX 6: APOC FUNDING REQUIREMENTS

In order to extend its phasing-out and exit period up to 2015, APOC is **now requesting an additional US\$46.4 million in donor funding**. Adding this US\$46.4 million to the US\$7 million shortfall carried over from the 1996–2010 budget gives a **total funding gap of US\$53.4 million** for the 2008–2015 period. The additional time and funding are required for the following 3 reasons: The approved budget for APOC operations over the **original Phase 1 (1996-2001), Phase II (2002–2007) and Phasing-out (2008-2010) periods amounted to US\$135 million**. As of 2007, US\$128 million has been pledged, of which US\$112.5 million has been received and spent and US\$15.5 million has been pledged but not yet been spent, leaving a **shortfall of US\$7 million still to be pledged**, a gap which has reportedly been filled during the duration of writing this report.

Fig.10: Diagram of APOC Trust Fund financial status 1996-2015



Sources

APOC. 2007. Plan of Action and Budget 2008 - 2015: Proposed Phasing-out and Exit Strategy, September 2007.

APOC. 2008. A Strategic Overview of the Future of Onchocerciasis Control in Africa, September 2008.