Università degli Studi del Piemonte Orientale

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Valentina Drago

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To

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Contents

1. Neglected tropical diseases

Neglected tropical diseases (NTDs) are defined as ancient, disabling, and poverty-promoting chronic conditions that afflict the poorest people in the developing world (1). NTDs have common features, which include high endemicity in rural and impoverished areas of Low-Income Countries (LICs), as well as the impairment of childhood growth, education, and worker productivity (2). The term “neglected” is the best way to define these kinds of diseases that have being ignored in spite of their socioeconomic burden. In fact these diseases occur among the poorest people where there is no sufficient access to medicine or medical help. So far the World Health Organization (WHO) has identified 17 NTDs (table 1.1) resulting from four different causative pathogens, endemic in 149 countries and affecting more than 1.4 billion people.

Table 1.1 The 17 NTDs, according to WHO (3).

Pathogens causes	Diseases
Virus	Dengue/severe dengue Rabies
Protozoa	Chagas disease Human African trypanosomiasis (sleeping sickness)
Helminth	Cysticercosis/Taeniasis Dracunculiasis (guinea-worm disease) Echinococcosis Foodborne trematodiases Lymphatic filariasis Onchocerciasis (river blindness) Schistosomiasis Soil-transmitted helminthiases
Bacteria	Buruli ulcer Leprosy (Hansen disease) Trachoma Yaws

NTDs affect the lives of about a billion people around the world, especially in the African regions, and threaten the health of millions of people. NTDs are chronic disabling conditions that kill an estimated 534,000 people every year and cause about 62.5 million disability-adjusted life-years (DALYs) (2,3). However, due to the nature of the diseases, the lack of sufficient disease surveillance and consequently the underestimation of disease incidence, the real burden of NTDs is not easy to estimate.

DALY is a time-based metric explained for the first time in the Global Burden of Disease (GBD) 1990 study that measures the gap between an "ideal" healthy population and the reality caused by a specific disease, combining both premature mortality (years of life lost, YLLs) and disability (years of life lived with a disability, weighted by the severity of the disability, YLDs):

DALY=YLL+YLD (4). YLL takes into account both the frequency of deaths and the age at which it occurs. It is calculated from the number of deaths at each age multiplied by a global standard life expectancy at the age when death occurs. Disabilities are differently weighted so that more severe is the disability greater is the number of YLDs that are lost; disability weight is comprised between 0 and 1, where 0 corresponds to perfect health and 1 to death (5).

NTDs, thanks to existing and cost effective medicines as well as the application of simple and basic healthy habits, are preventable and eradicable diseases; however, medicines are not always available and healthy habits are not so well known among the poorest people affected by NTDs (6). This can be understood from the fact that during the period 2000-2011, only 37 of the new 850 therapeutics products (including vaccines, biological, fixed-dose combinations, new indications, new formulation, new chemical entities), which account for 4% of the total products, were approved for neglected diseases. Moreover, in the same period just four of the 336 new chemical entities approved were for neglected diseases (7). These data are in line with the evidence reported in the study conducted to scrutinize pipelines for NTDs between 2005 and 2012. According to this report, only 650 clinical studies were conducted for NTDs, not numerically comparable with pipelines addressing influent diseases (e.g. 15,232 clinical trials for cardiovascular diseases and 10,063 clinical trials for respiratory diseases). The study also reported a growing number of trials in the period 2011-2012, and diseases like leishmaniasis, dengue, rabies, and salmonella were the most investigated (8).

Recently, more efforts have been made to tackle these debilitating diseases that are being recognized as major public health problems. The WHO recommends the simultaneous implementation of five public-health strategies for the prevention and control of NTDs (3):

- Preventive chemotherapy;
- Intensified case-management;
- Vector control;
- Safe water, sanitation and hygiene provision;
- Veterinary public health.

The need to tackle NTDs was embraced by governments and donors, including the pharmaceutical companies and nongovernmental organizations (NGOs), investing in preventing and controlling this diverse group of diseases. In January 2012 two important events strengthened the attention being given to NTDs and their eradication (by 2020): the London Declaration with the help of 22 partners, including WHO and the major pharmaceutical companies committed to sustaining the eradication of 11 of 17 NTDs; and the WHO programme entitled "*accelerating work to overcome the global impact of neglected tropical diseases; a roadmap for implementation".* The purpose of these interventions is to guide and implement strategies and policies, highlighting the importance to put an end to NTDs by the end of 2020 (9).

Even if the attention to these diseases in recent years has grown even more becoming a major public health issue, the efforts started at the end of the '80s, when the private and public sectors have merged to create a cost-effective, feasible and effective collaboration: the Public-Private Partnerships (PPPs).

PPPs are recognized as being useful because they combine drug donations from the private sector with the public intervention for administrating, advocating and coordinating activities at local level. These particular diseases need the implementation of different activities that require a broader intervention.

PPPs can intervene at different levels, depending on the issue to address. They have been established to either develop a new product for unmet needs or subsidize a product to control a specific disease, thus strengthening health

interventions. Medicine for Malaria Venture, International AIDS Vaccine Initiative, and the Global Alliance for TB Drug Development are examples of PPPs established to fund research in developing medicines for specific diseases *(10)*.

PPPs have also been implemented to address NTDs through specific drug donation programmes (DDPs), adopting strategies aimed at reaching the greatest number of people affected and eradicating the disease. DDPs have been applied in different contexts, including short-term responses to emergencies, such as natural disasters, donations of existing inventory and donation in response to specific diseases *(11)*. DDPs represent a sustainable way of donating a specific treatment, applying vertical programmes (also known as stand-alone, categorical or free-standing programmes or the vertical approach) to enable medicine access especially in the case where drug costs are not affordable, and donations by private sector represent the only solution *(12)*. Vertical health programmes refer to instances where "the solution of a given health problem is addressed through the application of a specific measure through single-purpose machinery"*(13)*. On the contrary, integrated programmes (also known as horizontal programmes, integrated health services or horizontal approaches) seek to "tackle the overall health problems on a wide front and on a long-term basis through the creation of a system of permanent institutions commonly known as general health services" *(14)*. In recent years, the debate has been focused on identifying which kind of strategies, between vertical and integratated programmes, is better to apply in the case of NTDs to finally eradicate them.

Through DDPs Mass Drug Administration (MDA) strategies have been implemented, allowing the distribution of medicines donated by pharmaceutical companies or provided at discounted cost on a large-scale *(15,)*. When

applicable, MDA is also adopted for the realization of Preventive Chemotherapy (PC), first introduced by WHO to prevent transmission or morbidity of human helminth diseases through drugs distribution (16), and subsequently adopted by DDPs.

PC is characterized by (i) population-based diagnosis, (ii) population-based treatment and (iii) implementation at regular intervals (17).

Africa is the most affected area by NTDs, in both the sub-Saharan Africa regions and many other tropical and subtropical areas where there is an overlap of NTDs; at least five to six neglected tropical diseases occur in the same region, leading to a polyparasitized population *(18)*.

Trachoma, LF, onchocerciasis, schistosomiasis and the three major soil-transmitted helminths diseases (STHs), including ascariasis, trichuriasis and hookworm) are the seven mostly widespread NTDs in Africa that exhibit considerable geographic overlap. Therefore, they can be controlled and in some cases eliminated by four effective treatments through MDA, applying PC on a large-scale: ivermectin, albendazole, azithromycin and praziquantel (2,18). These treatments are currently donated through PPPs already operating in parallel in Africa: ivermectin for the treatment of both onchocerciasis and LF, that is also effective against *Ascaris* and *Trichuris* infections, and represents the standard treatment for human strongyloidiasis; albendazole is used for the treatment of LF, STH and hookworm; azithromycin is effective in tackling trachoma; and praziquantel is used for schistosomiasis and STH. The overlapping of these NTDs and the possibility to control them with just four treatments gives the chance to establish integrated control programmes. In addition, the four-drug regimen would also target ectoparasite infections, such as scabies, pediculosis, tungiasis, and cutaneous larva migrans, and their resulting secondary bacterial skin infections *(19, 20)*.

For the control and elimination of these selected diseases, WHO recommends implementing PC as an effective strategy, integrating it with other interventions such as: management of morbidity; vector and intermediate host control; provision of safe water supply, sanitation and hygiene *(9)*.

The most important DDPs managed through PPPs are representing by the Mectizan Donation Programme (MDP), the Global Programme to Eliminate Lymphatic Filariasis (GPELF), and International Trachoma Initiative (ITI).

The MDP is a PPP that donates ivermectin, thanks to the contribution of Merck, for the control of onchocerciasis and LF where they are co-endemic. The GPELF distributes albendazole for LF donated by GlaxoSmithKline (GSK), that is also donated by MedPharm through the Schistosomiasis Control Initiative, a PPP based in London and operating locally in different countries in Africa, that distribute albendazole in combination with praziquantel regimen *(21)*.

So far, the PPPs seem to be an effective strategy to overcome NTDs. MDP is the first DDP established through a PPP, founded in 1987 by Merck & Co. for the distribution of ivermectin (Mectizan®) *"wherever is needed for as long as needed"* primarily for the control and subsequently for the elimination of onchocerciasis *(22)*.

In response to the WHO call to eliminate blinding trachoma by 2020 (GET2020), the ITI was founded in 1998 thanks to the contribution of Pfizer, the donor of azithromycin (Zithromax®), and the Edna McConnell Clark Foundation.

In 2000 the WHO launched the GPELF; this initiative was embraced by GSK, who decided to collaborate with WHO donating albendazole (Albenza®) for the control of the disease, followed by Merck who contributed with ivermectin donation in the co-endemic countries *(22, 23)*.

Based on the *WHO plan for accelerating work to overcome the global impact of NTDs*, onchocerciasis falls into diseases group for which eradication in Latin America is feasible by 2015; the elimination of trachoma and LF are expected by 2020, estimating the elimination of blinding trachoma in 75% of countries affected, and the 100% of elimination in the case of LF *(9)*.

Other important examples of DDPs founded to overcome NTDs are: Children without Worms for global control of STH, established in 2006 by the Task Force for Global Health and Johnson & Johnson who committed themselves to donating up to fifty million doses of mebendazole annually (24); since 2000 Novartis in collaboration with WHO supports the global fight against leprosy, donating multidrug packages of dapsone, rifampicin, and clofazimine (25). In 2001 Sanofi Aventis decided to collaborate with WHO, donating multidrug therapy packages of pentamidine, melarsoprol, and eflornithine for the treatment of sleeping sickness (26).

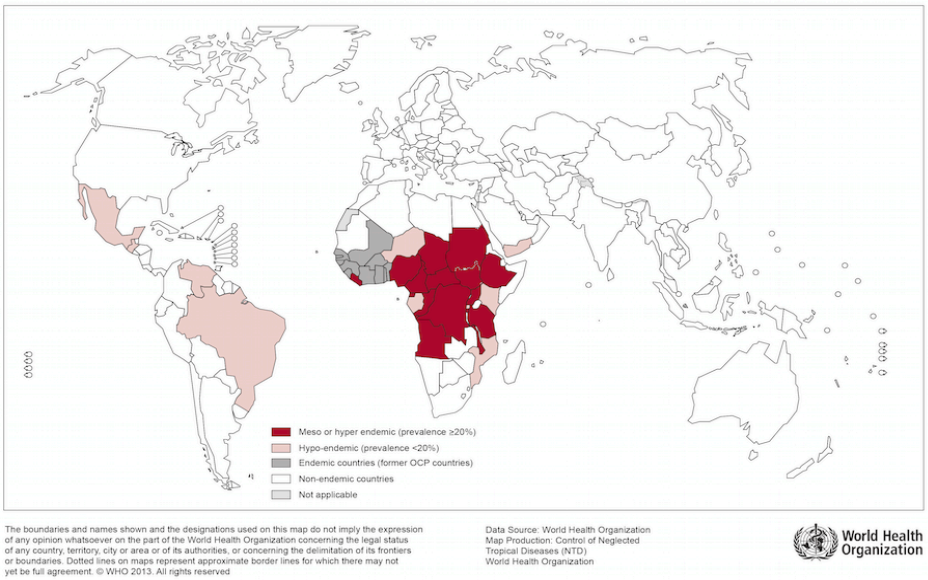
1.1. The drug donation programme based on PPPs

1.1.1. The Mectizan Donation Programme

Onchocerciasis, also known as river blindness, is a parasitic disease caused by the filarial worm *Onchocerca volvulus* that affects eyes and skin, transmitted through the bites of infected *Simulium* blackflies. The parasites that cause onchocerciasis are transmitted from human to human, and adult *onchocerca volvulus* worms can live for fifteen years in the human body. Prevention is based on vector control to kill the larvae of the blackfly vector using environmentally safe insecticides. It is a major cause of blindness in many

African countries, representing the world's fourth leading cause of preventable blindness after cataracts, glaucoma and trachoma, and the second largest cause of infectious blindness. It also causes ugly skin disfigurement with depigmentation, severe itching and swelling that have serious socio-cultural implications. The manifestation of the disease includes impaired vision, blindness and chronic dermatitis. Definitive diagnosis of onchocerciasis is made by examination of skin biopsies for microfilaria. The treatment of onchocerciasis is based on a single yearly dose of ivermectin (Mectizan®). Africa represents the most afflicted region for onchocerciasis, where 99% of people infected by *O. volvulus* live in 31 sub-Saharan African countries; another 12 foci were found in 5 regions of Latin America: Brazil, Ecuador, Guatemala, Mexico, Venezuela *(27)*. According to these latest data, onchocerciasis is estimated to be endemic in 37 countries *(28)*. The impact of onchocerciasis includes lost economic productivity, diminished earning, adverse effects on the demand for labour, and reduced agricultural output.

Figure 1.1 Distribution of onchocerciasis worldwide, 2013.



(29).

Ivermectin is an anthelmintic agent for oral administration indicated in the treatment of onchocerciasis caused by *O. volvulus,* as well as for the treatment of microfilaremia caused by *Wuchereria bancrofti infection*, the causative agent of LF. The recommend dose is annual or twice yearly to all non-pregnant adults and children <15 Kg (*30).*

In response to this emergency situation, in 1987 Merck decided to donate ivermectin for the treatment of onchocerciasis for as long as necessary wherever it is needed. In 1998 Merck expanded its donation for the treatment of LF in 28 African countries and in the Yemen where onchocerciasis and LF resulted co-endemic (31*).* With this aim in mind, MDP was born, a PPP that resulted in a multisectoral coalition between Merck & Co., the Mectizan Expert Committee (MEC), the Task Force for Child Survival and Development, WHO, the World Bank, the United Nation Children's Fund (UNICEF), National Ministries of

Health (MoH), more than 35 non-governmental development organizations, and thousands of local community health workers *(32)*.

The MDP built up a strong governance both at central and local level. At international level the MDP Secretariat and the Mectizan Expert Committee are present, ready to collaborate with regional coordination programs in Africa and America *(33)*.

The principal purposes of the program are:

- Assure availability of ivermectin for the treatment of onchocerciasis;
- Provide good medical practice;
- Approved prescribing procedures, including the monitoring of adverse reactions.

These aims have been implemented adopting and supporting MDA, vector control, surveillance, reports and advocacy about activities.

In order to manage the drug distribution and collateral activities with the intervention of local bodies, the Onchocerciasis Control Programme in West Africa (OCP) was born (1974-2002), the African Programme for Onchocerciasis Control (APOC) was launched in 1995, and the Onchocerciasis Elimination Program for the Americas (OEPA) begun in 1992. These programmes are all still operating *(33)*.

The OCP was established between WHO, World Bank, the UN Development Programme, the UN Food and Agriculture Organization, NGOs and more than 25 donors. It succeeded in eliminating onchocerciasis as a public health problem adopting vector control through insecticides and drug distribution in 10 African endemic countries.

APOC is a partnership between donors, NGOs, the UN agencies and member countries, with the WHO as the executive agency, MDP as provider of ivermectin, and the World Bank as a fiscal agency. The aim is to establish

within a period of 15-20 years, an effective and self-sustainable community-directed treatment (CDT) in the endemic areas of the 19 member countries, principally for morbidity control. More recently APOC fixed the new goal of eliminating onchocerciasis where possible by 2025 (34). In 2012, APOC estimated that 76.4% of the at-risk population had been covered by ivermectin treatment (35). CDT is a project conceived in 1996 thanks to the intervention of WHO, World Bank, and Special Programme for Research and Training Disease, with the collaboration of African scientists, in order to find a more sustainable and cost-effective method for treatment delivery. CDT was formally implemented for the first time in 1997 by APOC. According to an APOC report, 447 million doses of treatment have been administered, and CDT projects are operated in 91% of the APOC area, protecting 96% of the 94 million people targeted with an overall treatment coverage of 89% *(36)*. Both Colombia and Ecuador interrupted transmission of river blindness in 2007 and 2009 respectively. In 2011 also Guatemala and Mexico stopped transmission (28).

Along with the distribution of ivermectin, MDP adopted different tools specifically implemented for onchocerciasis. In response to the need of APOC to determine the exact geographical distribution of onchocerciasis, WHO's Special Programme for Research and Training in Tropical Diseases (TDR) developed a rapid assessment method in 1993, the Rapid Epidemiological Mapping of Onchocerciasis (REMO). It based on geographical information, especially on the presence of river basins, to identify communities likely to be at a high risk of infection. Using REMO, it is possible to define the hyper and meso-endemic areas where the community nodule prevalence is ≥ 20%. This was followed by other tools for mapping the disease to predict high risk communities by dividing areas into bioclimatic or biogeographic based on the

distance from breeding sites; one of these is the Rapid Epidemiological Assessment (REA) that establishes treatment priorities by counting nodules. OCP and others found that the prevalence of nodules in a cohort of adult males multiplied by 1.5 is a reasonable estimate of the community prevalence of onchocerciasis while the Rapid Assessment for procedure for Loa Loa (RAPLOA) was developed by UNICEF, TDR, United Nation Development programme (UNDP) and financed by APOC. RAPLOA based on a questionnaire on the history of visible worms moving in the lower part of the eye, predicting whether or not loiasis is present at high levels in a community *(33)*.

More than others, CDT represents the most important intervention that makes the distribution of ivermectin feasible and reachable also among the remotest areas of endemic countries. MDP is the first program that has been able to improve delivery strategies, starting from passive distribution (where drugs were delivered at the health centers), through mobile teams (where paid local health professional are responsible for drug distribution), to community-based distribution (CBD), and the CDT called, in the case of ivermectin distribution, CDTI. This last strategy represents a milestone in the DDPs, because the result was a cost effective intervention able to involve communities in the distribution of treatments, enhancing their consciousness about the disease and the importance of treating it. CDTI represents the main pillar of drug distribution, because it implies the involvement of communities also at decision level (37.)

In the case of ivermectin, once a community has decided to adopt the CDT, the MoH and NGOs train a health worker; in turn, the health worker runs a training programme for the community that institutes their own Community-Directed Distributor (CDD), who is trained to:

- Use measuring sticks to estimate how many ivermectin tablets to give;

- Detect and treat minor side effects;
- Refer cases of severe adverse events to the nearest health facility;
- Fill in household treatment forms;
- Keep records;
- Report about the treatment campaign;
- Know the criteria for exclusion to ivermectin treatment;
- Organize the storage and management of the ivermectin tablets *(38)*.

In terms of drugs delivered, thanks to the MDP between 1,5 billion treatments for onchocerciasis have been donated, treating about 700 million people, from when it was started to 2012 *(39, 40)*. The achievements of MDP can be understood through the activities carried out by the two organizations that independently operated in Africa: OCP and APOC. The activities of OCP, that among the others also includes advocacy, community support and drug distribution, were successful in preventing blindness in 600,000 people, reducing the level of infection in 40 million blind people and reclaimed 250,000 km2 of abandoned land *(27)*. In 2006, thanks to OEPA, the 13 foci of regions where the program is operated achieved more than 85% of ivermectin coverage, and transmission was interrupted in 10 out of 13 foci by the end of 2011 *(41)*.

In the APOC area over 100 million people received regular treatment for onchocerciasis by the end of 2012. Since inception, the programme has recorded an 86% reduction of unrelenting itching, 39% reduction in infection prevalence of the disease, prevention of more than 500,000 cases of blindness and an estimated economic rate of return (ERR) of 17% on invested funds. ERR is often calculated as the Net Present Value (NPV) of the stream of net benefits equal to zero. If the ERR is greater than the market interest rate or the cost of borrowing money, then the programme is determined to be an economically worthy investment (42). En ERR of 10% is considered by the World Bank as a

standard for successful public health programmes (43). About 185,000 communities distributed ivermectin, representing an overall geographic coverage of 95.4%, and the prevalence of infection has been reduced by about 73% compared with pre-APOC levels. Annual treatment with ivermectin in APOC countries has increased from 1,5 million in 1997, to 68.4 million in 2009, nearing the projected target of 90 million by 2015 *(36)*.

Referring to the year 2000, OCP spent a total $13.9 million in 11 countries in West Africa; among these vector control is the component that influences to a major extent accounting for $9.2 million.

In the same year the total costs of APOC were estimated at $9.4 million in 19 member countries throughout Africa, where $5.9 million of this amount was spent on national ivermectin distribution projects, carried out in 13 of 19 APOC countries.

While a significant portion of OCP expenditure was for vector control, for APOC's activities this represents a minimal part.

The cost effectiveness of APOC activities was calculated at US$14-$30 per DALY averted. However, the economic benefit is sensitive to the fact that the drug has been donated free of charge. (42). WHO has found that treatment cost of ivermectin is US$0.57 per person, yielding a 17% ERR.

Based on cost data collected in savannah foci in Ghana, it was estimated that the economic cost of annual CDTI is $41,536 per target population of 100,000 individuals per year (2012 prices) *(34)*.

The sustainability of MDP and CDTI has been assessed much more than other programmes and activities, both in quantitative and qualitative studies.

A recent study estimated APOC financial cost between 1995 and 2010, excluding cost of drugs. MDA with ivermectin averted 8.2 million DALYs (3.2 million due to itch, 4.4 million due to blindness, 0.6 million due to visual

impairment) in APOC areas, at a nominal cost of about US$257 million. The study analyzed data on pre-control prevalence of infection and population coverage of mass treatment, simulating trend in infection, visual impairment, blindness, and severe itch through the micro-simulation model ONCHOSIM. According to calculations, MDA against onchocerciasis accounted for about a nominal US$31 per undiscounted DALY averted between 1995 and 2010. If expected health gains and costs for the period 2011-2015 are included, mass treatment accounts for $27 per DALY averted. According to WHO guidelines, this is highly cost-effective, as it is below the GDP per capita of most countries covered by APOC (27-1,545 international dollar per capita, Global health Observatory Data Repository, accessed 2 August, 2012). These results indicate that cost per treatment with ivermectin in APOC areas is affordable, at US$0.51 per treatment, excluding cost of donated drugs *(44)*.

Remme and colleagues estimated that the predicted cost of CDTI in APOC countries during 15 years of activities was US$145 million referring to international donor community plus US$64 million referred to MoH, giving a total US$209 million. They estimated that the CDTI cost (excluding drug costs) is approximately US$7 per DALY averted. Assuming that 70% of endemic communities will ultimately be covered by CDTI and 80% of those communities will maintain annual treatment at 65% coverage for at least 15 years, at least 26 million DALYs would be prevented over a 25-year period (45). Conteh estimated that CDTI cost US$9 per DALY averted; Laxminarayan reports that CDTI costs US$6 per DALY averted, when the drug has been provided free of charge. *(46, 47)*. Onwujekwe et al conducted a study in the villages of Nike and Achi in Nigeria they estimated treatment cost to be $0.17 and $0.13 per dose in the two villages, respectively. These estimates include the

direct financial costs, opportunity costs, advocacy, mobilizing the community, training and distribution (48).

Onchocerciasis is the fourth leading cause of blindness worldwide, having a huge socioeconomic impact among populations. Blindness, visual impairment and onchocercal skin disease (OSD) primary impact in lost productivity, diminished earnings both among people affected and among caregivers, adverse effects on the supply of labour, and reduced agricultural output due to the exodus from arable land (46). This can be defined through the data emerged in the multicountries study conducted in 1997 by the World Bank on the economic impact of the OSD, including two sites in Nigeria and one in both Sudan and Ethiopia respectively. This study is based on a matched-pair prospective design comparing OSD and non-OSD persons, including the costs of health-related expenditures at individual and community levels, productivity, transportation, non-cash exchanges, and time spent in seeking health care and accompanying patients. From the study it emerged that on average, persons suffering from OSD were found to spend an additional $8.10 over a 6-month period in comparison to their non-OSD counterparts from the same community, and spend an additional 6.75 h seeking health care over the same 6-month period. The average per-capita annual expenditures for health in Nigeria, Sudan and Ethiopia are $23, $48 and $25 respectively *(50)*. These results are comparable with data obtained in the study conducted by *Kim* in 1997, on the earnings of 425 permanent workers of Teppi coffee plantation in southwest Ethiopia. Data emerged showing that those workers who are not affected by OSD earned on average $5.32 in 2001 US dollar more per month than workers with severe OSD. This difference was statistically significant ($P< 0.05$). The amount represents 5.2% of GDP in Ethiopia. Workers with OSD lost an average 1.9

days of work per month in comparison with who are not affected by the disease *(42)*.

Amazigo et al in 2007 conducted a study to evaluate the performance of the communities under the CDTI activity, with particular interest in determining whether or not the community participation and ownership really existed in the CDTI project development. They defined ownership as follow: *"evidence of the ability of the community to own and manage CDTI; participation of community members and their leadership in decision-making; initiating and supporting CDTI implementation"* (*51)*. When this study took place there were 41 projects in 10 countries that had distributed ivermectin through CDTI from three to five times over a set period, and all of these projects are included in the study.

Much of the information about community level was collected in situ, using semi-structured interviews with community members, CDDs and their leaders, and/or from direct observation. Other information was collected also at higher levels, including health facility support indicators. For each country evaluation members came from both internal and external levels, including the CDTI project coordinators from the regional and/or district levels of the health system, onchocerciasis researchers, specialists from the NGDO coalition, and representatives from the donors. The evaluation was based on nine community-level sustainability indicators and relative evaluation instruments.

To assess the routine project activities and process:

- *Planning:* evaluate planning and managing of CDTI by CDDs and community authorities;
- *Leadership:* evaluate how community leaders managed problems associated with distribution and evaluation of communities involvement in key decisions;

- *Monitoring &Supervision:* evaluate whether CDDs reported complete and accurate distribution data;
- *Mectizan Supply & Distribution:* evaluate whether the drug was obtained and managed effectively by the community;
- *Training, health education, sensitization, advocacy, mobilization (TRHSAM).*

To assess resources available to projects:

- *Financing:* evaluate whether the community supported the CDDs and CDTI;
- *Human resources:* evaluate the willingness to help by the community members;
- *Transport and material resources:* evaluate the transportation of Mectizan provided by community.

To assess the therapeutic coverage:

- *Coverage:* the proportion of eligible population who had received ivermectin in a given year. (65% being the threshold required to achieve control within 15 years).

For each project, the performance of the community and health care providers were rated using qualitative and quantitative indicators predicting sustainability. Each indicator is scored from 0 when no progress has been made toward sustainability, and scores between 1 and 4 indicate slight to full progress toward sustainability. The result showed that at community level, over 70% of projects received satisfactory sustainability scores of 2.5 or more. It is important to highlight that sustainability indicators had the highest score when communities had the most control; by contrast, the indicator where communities depended on government health systems, were scored below 2.0 points by communities (*51).*

Another qualitative study was conducted by *Burnham and Mebrahtu* in 2004 in order to clarify organizational structures and governance functions using semi-structured interviews with key informants and self-administered survey of staff involved, among 21 international organizations and 34 individually staffed persons. They received completed surveys from 25 persons using a survey based on the four-point *Likert* scales, ranging from 1 (no benefit) to 4 (major benefit). The objective of the study is to assess the benefits, problems, costs, governance and management of the MDP from the partner's viewpoint. Three important factors emerged when analysing the institutional relationships among the partners that contributed to the success of the programme:

- Each participating organization perceived benefits from its collaboration with the other institutions involved in the program;
- The relationship between Merck and MDP has been characterized by transparency and communication, and the visibility and credibility of the MDP's first chairman strengthened the relationship with Merck and other organizations;
- The clear separation of Merck's role in providing and shipping the drug from Expert Committee and Secretariat's role of providing technical expertise and management of the donation program *(33)*.

The key issues raised from this qualitative evaluation are the following:

- *Gender:* despite the efforts of APOC to encourage women to take part in the implementation of community distribution, the majority of community-selected distributors tend to be male;
- *Treatment costs:* from the inception of MDP, Merck tried to provide ivermectin free of charge, but this was not always possible. It was feasible just where delivery systems were largely publicly funded, as in

Latin America or when MDA has been part of a multinational programme as in the case of OCP. Where cost recovery systems were subsidized by national policy, the MDP decided to allow charges for the delivery of ivermectin, maintaining the drug at no cost. The APOC has taken a position against paying incentives for distribution, encouraging communities to support distributors directly;

- *Records:* one of the major difficulties experienced in APOC areas has been the inability to obtain accurate community census data to provide the denominator in the calculation of ivermectin coverage rates;

  Monitoring: in OCP countries a strong monitoring program was in place from the beginning, and there was a good data management capacity built by the WHO/OCP. The data flow begins with treatment reports sent by the community distributors to the health facility level where they are summarized. NGOs play a key-role in motoring programs, particularly where first-line health facilities are weak or absent. At the APOC level, it is planned that monitoring teams visit country projects twice during their 5-year cycle to assess progress towards achieving objectives. Community-based monitoring approach is a good one to be developed *(33)*.

1.1.2. International Trachoma Initiative

Trachoma is an infectious disease caused by *Chlamydia trachomatis* that is responsible for about 3% of cases of blindness worldwide. It still represents the most common infectious cause of blindness worldwide. According to WHO's

estimation, 7.3 million people have trichiasis (eye lashes touching the cornea); 229 million people are at risk of infection worldwide, and 21 million of active cases have been estimated. In endemic areas more than 21 million people need antibiotic treatment, about 7 million people required surgery and 2.2 million are visually disabled, of whom 1.2 million have become irreversibly blind *(52)*. Trachoma is a chronic disease, characterized by repeated or persistent infection of the superior tarsal epithelial cells of conjunctiva. The diagnosis of the disease is possible through rapid and efficient laboratory methods not available in the endemic countries, so the diagnosis is usually made clinically. To simplify the detection, WHO developed a grading system based on signs and the extent of the inflammation, conjunctival thickening and scarring, trichiasis, and corneal opacity, based on five different stages:

- 1st: Trachomatous Inflammation-Follicular (TF): the presence of five or more follicles in the upper tarsal conjunctiva.
- 2nd: Trachomatous Inflammation-Intense (TI): pronounced inflammatory thickening of the tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels. The TF and the TI stages are also defined as Active Trachoma.
- 3rd: Trachomatous Scarring (TS): the presence of scarring in the tarsal conjunctiva.
- 4th: Trachomatous Trichiasis (TT): defined as at least one eyelash rubbing on the eyeball.
- 5th: Corneal Opacity due to trachoma (CO): easily visible corneal opacity over the pupil.

Active Trachoma as Trachomatous Inflammation-Follicular and /or Trachomatous Inflammation-Intense (TF/TI) were also defined within this ranging system *(53)*.

According to latest data, 51 countries are known or suspected to be endemic to blinding trachoma in Asia, Central and South America, Australia and the Middle East. Africa has the higher prevalence, accounting for the 77% of prevalence worldwide: of the 46 African countries, 29 are thought to be, or have been endemic and report the major numbers of cases of trachoma: 18.2 million cases of active trachoma (representing the 85.3% of all cases globally) and 3.2 million cases of trichiasis (44.1% of all cases globally). Ethiopia and South Sudan have been reported the highest prevalence. *(54)*.

Figure 1.2 Distribution of trachoma worldwide, 2012.

(55).

ITI is PPPs that support the WHO initiative called the Alliance for Global Elimination of Trachoma by the year 2020 (GET2020), and it is also a member of the Global Alliance Vision 2020: the Right of Sight. The activities of ITI are

focused on strengthening national trachoma control programs, collaborating with national institutions, NGOs agencies and partners with the aim of eliminating blinding trachoma by 2020. As for the MDP, also the ITI was able to structure the governance at central level with the Board of Directors, the ITI Secretariat and the Trachoma Expert Committee (TEC), an independent body of seven internationally recognized experts in the field of public health, ophthalmology, blindness prevention and SAFE strategy implementation *(56)*.

The principle mission of ITI based on the distribution of azithromycin, implementing the "A" component of the SAFE strategy, promoting surgery for trichiasis (the advanced stage of trachoma), providing technical assistance and mobilizing resources for trachoma control programs.

The SAFE strategy was launched in 1997 by WHO, and includes:

- Surgery for trichiasis: directed at the TT stage of the disease, the immediate precursor of blindness. Ophthalmic assistants and nurses could perform the simple and quick surgery procedure after a training period of 2 weeks, using local anesthetic. The procedure itself takes about 15 minutes and long-term success rates are around 80% *(57)*.
- Antibiotic azithromycin: antibiotic is used for active disease, TF or TI stages. Before the introduction of Zithromax, the treatment was based on a topical preparation of tetracycline, however the ointment must be applied to the eye twice a day for 6 weeks. Trachoma control programmes use antibiotics for two reasons: first, to treat individually infected people, and secondly, to limit transmitting the infection to others. Because many people who are infected do not have signs of the disease on examination, mass treatment of all individuals living in a community seems a good approach to reduce the transmission of infection where the disease is endemic.

- Facial cleanliness: this approach is helpful to break the cycle of reinfection and helps to stop the spread of disease, especially among children. Despite the previous components, this, and the environmental improvement approach are focused on preventing transmission.
- Environmental change to increase access to water and sanitation: the disease is known to be highly correlated with poverty, lack of personal and community hygiene, limited access to healthcare and water. Interventions include provision of water and control of flies (57).

Azithromycin donation is feasible thanks to the contribution of Pfizer; it is a macrolide antibiotic for oral administration, effective in a single dose therapy (20 mg/kg body weight), and represents the first-line antibiotic chosen for the treatment of trachoma due to *Chlamydia trachomatis bacterial.*

The application process for azithromycin is started nearly eighteen months before the drug arrives in the recipient country. ITI works directly with national trachoma program managers who are nominated by the MoH *(58*).

The distribution of antibiotics is made through MDA. WHO has developed guidelines for drug distribution, firstly based on determining the prevalence of follicular trachoma at district-level in children with 1 to 9 years old. If the prevalence of active trachoma (1st or 2nd stages of trachoma) is 10% or higher, mass treatment with antibiotics must be carried out on all people throughout the district, and should continue for at least 3 years and should not stop until the prevalence of TF in children aged 1-9 years is below 5%. If the baseline prevalence is 30% or more, annual treatment should be undertaken for at least 5 years before review. Where the prevalence falls below 10%, treatment is recommended only in those communities with a prevalence ≥10% (*59).*

Along with the donation of azithromycin, ITI holds several activities that support the drug donation:

- Collaborating with MoH, governmental and NGOs, to support the "A" element;
- Promoting Surgery for trichiasis, "facial cleanliness" and "environmental improvement";
- Providing technical assistance to countries and partner organizations, including logistical assistance;
- Mobilizing resources for trachoma control programmes;
- Integrating trachoma control into approaches to control and eliminate the other NTDs;
- Advocating for trachoma to be included in a wider programmes at global level .

Despite the involvement of international bodies, it has been recognized that most countries have not yet implemented programmes to eliminate blinding trachoma by 2020. In order to meet these gaps, a new tool has been developed, the Trachoma Action Plan (TAP). TAP represents a useful template that was able to delineate specific actions to undertake and milestones to reach by individual nations. To date, this has been successfully implemented in most trachoma endemic countries in Africa *(60)*.

Even though efforts have been made to eliminate trachoma by 2020, the estimation of trachoma distribution represents, still today, a big issue that leads to an unrealistic epidemiology data about the disease. To overcome this obstacle, different tools have been developed for gathering data regarding the prevalence of trachoma, to find out the geographical distribution of trachoma, of primary importance for planning, implementing, monitoring and evaluating the trachoma control programmes *(61)*.

These tools include:

- Trachoma Rapid Assessment Method (TRA);

- Population-based Prevalence Surveys (PBPS);
- Acceptance Sampling Trachoma Rapid Assessment (ASTRA);
- Integrated threshold mapping (ITM).

TRA was developed by WHO as a rapid and inexpensive method used to determine community priority for treatment; although ASTRA is not widely used, it is useful to classify communities in relation to a threshold value.

PBPS is the most widely used method since it provides a representative measure of the prevalence of trachoma within a population. The ITM is the most recent method developed and takes into account sampling of school children, pre-school children and women of childbearing age to determine whether the prevalence of trachoma (also applicable to other NTDs) falls under a specific threshold *(61, 62)*.

National data indicates that about 45 million people were treated for trachoma in 2010, and 52 million in 2011, mainly using azithromycin plus tetracycline eye ointment *(61)*. Morocco represents the first country that achieved the Ultimate Intervention Goals (UIG) in 2006, eliminating trachoma. Gambia and Ghana are part of the African countries that are in the post-endemic surveillance stage *(63, 64)*.

According to WHO's latest data, the countries which have reported the successful outcome indicator targets are Gambia, Ghana, Iran, Morocco, Myanmar, Oman and Viet Nam. These outcome indicator targets for elimination of blinding trachoma as a public health problem are:

- <1 case of TT "unknown to the health system" per 1000 total population;
- Prevalence of active trachoma sign TF of <5% in children aged 1-9 years *(54)*.

Impact assessment data reported by ITI based on countries level data, highlight that where TF baseline prevalence is 30% and above in children aged 1-9 years, even 5 years of SAFE intervention is insufficient to reduce TF to less than 5%, and reduce the prevalence of TT in the whole population to less than 0.1% *(65)*.

In spite of the efforts made during the meeting of WHO GET2020 in 2011, it was recognized that most countries were not yet developing their plans to eliminate blinding trachoma by 2020 *(66)*. The lack of information about trachoma epidemiology derives form a lack of knowledge about the geographical scope of disease, therefore it is essential, and of great importance, to know where intervention is necessary. To plan surgery for trichiasis, as part of the SAFE strategy, it is essential to know the prevalence of trichiasis, and also the implementation of the other activities, including MDA, based on the recognition of the prevalence of active trachoma. With the aim of overcoming the knowledge gap about epidemiology data, not reachable through the tools which already exist, the project Global Trachoma Mapping Project (GTMP) has been funded. The team project works with MoH, and it is scheduled to end by 2015. Based on GTMP, each suspected endemic area is subdivided into "evaluation units" which contain 100,000-250,000 people. Then, a PBPS of more than 20 clusters is undertaken among each evaluation unit. Data are collected based on water and sanitation at household level, age, gender and presence or not of trachoma signs at individual level *(67)*.

After validation, obtained data are than collected and displayed on the web-based Global Atlas of Trachoma. It provides regularly updated, open-access district-level prevalence maps of the current status of trachoma prevalence *(68)*.

The year 2013 has been signed with an important progress toward the global MDA coverage. In fact, the global administrative coverage (the number of districts that received mass drug administration, divided by the number of

districts in which MDA was planned) was 83% (387/466), including 53 districts involved in antibiotic treatment for trachoma for the first time in 2013 *(54)*.

Through the ITI, during its first 15 years of activities, Pfizer has donated more than 340 million doses of azithromycin to 28 countries in Africa and Asia.

Evans conducted a cost effectiveness analysis of implementing trachoma control programmes in Myanmar, considering only direct costs. The study reports a total of US$54 per case of visual impairment prevented, and US$47 per case of visual impairment prevented including only non surgical costs (mostly antibiotic treatment) *(*69*)*.

Conteh estimated that the implementation of the strategy account for US$5-100 cost per DALY averted (46).

Frick and colleagues have made two different estimates about the economic cost of trachoma, framed in terms of lost productivity. The economic cost of one disabled person due to trachoma was calculated by multiplying the value of the disability weights by the individual economic productivity value for each country considered. In the first report the productivity lost was estimated at US$ 2.9 billion referring to the year 1995. The economic loss estimated in the second report was higher at US$ 5.3 billion referring to the year 2003, using the adjusted dollar value for 2003, considering the productivity lost from blindness to be 100% instead of 60% as in the first study and it added a 10% cost for each blind person for carers. The authors also examined the effect of including trichiasis and found that the lost productivity rises significantly to US$ 8 billion (*70)*.

In order to assess a qualitative evaluation of the ITI activities implementation, in 2001 the London School of Hygiene & Tropical Medicine (LSHTM) undertook an evaluation of ITI-supported trachoma control activities in eight countries: Ethiopia, Ghana, Mali, Morocco, Nepal, Niger, Tanzania, and

Vietnam. The aim of this project was to conduct participatory evaluations in the eight countries selected, in order to evaluate the effectiveness, efficiency, adequacy, and impact of the four components of the SAFE strategy.

Semi-structured interviews were conducted at central level, focused on gathering opinions about the strengths and weaknesses of the programme, in particular its structure and planning; instead the interviews conducted at regional and district levels were focused on the analysis of strengths and weaknesses of the implementation of the programme.

This study reported that a major obstacle to programme planning is lack of detail about trachoma endemicity. With the exception of Morocco, the national coverage of trachoma control activities, including antibiotic distribution, was insufficient compared with the magnitude of the disease burden. High-quality mass distribution of antibiotics was observed in most countries even in extremely resource-poor settings. The antibiotic coverage within communities generally exceeded 80%, and this appeared to be due in part to the high community acceptance of antibiotics. Inadequate water and sanitation remained a major problem in all programmes areas, in each of the countries. Monitoring of SAFE activities was generally poor, either because the indicators collected were inappropriate, or because systems were not in place for reporting from the community to the district, and on to national level *(71)*.

1.1.3. Global Programme to Eliminate Lymphatic Phylariasis

LF, also known as elephantiasis is one of the oldest and most debilitating NTDs. It is caused by the filarial nematodes *Wuchereria bancrofti, Brugia malayi or Brugia timori*. In 90% of cases, LF is caused by *W. bancrofti,* the

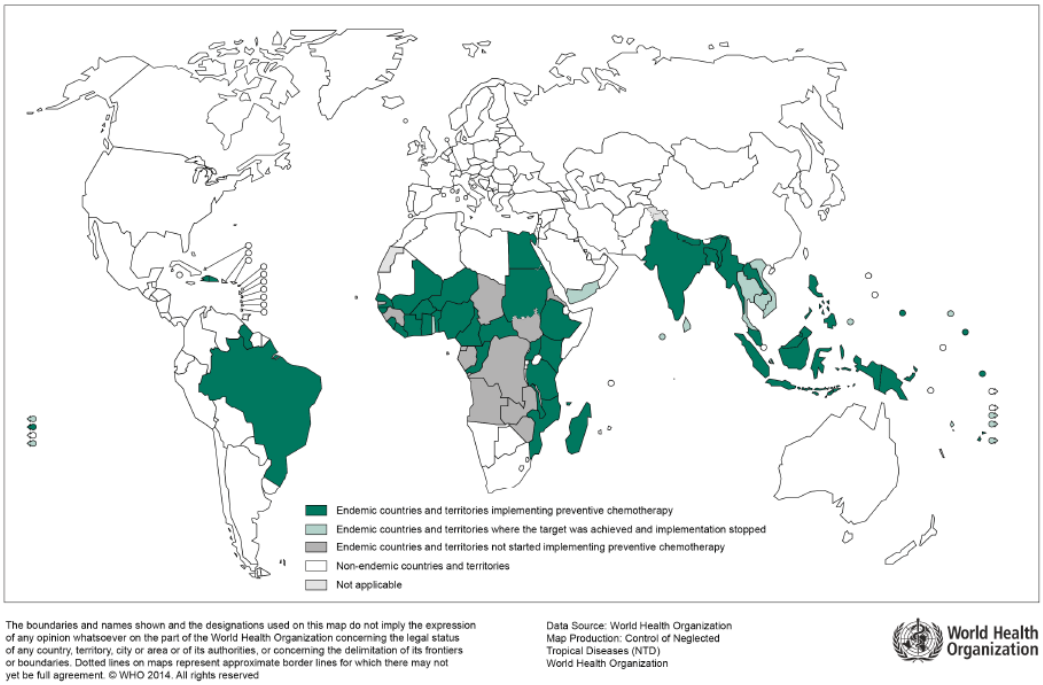
most diffused in Africa, transmitted to humans through the mosquito's bites *(72)*.

Although LF rarely causes death, it is a major cause of suffering and disability, leading to painful and disfiguring chronic enlargement of arms and legs, comprise children, representing the secondo cause of disability worldwide. The disease can result in different kinds of manifestations: adenolymphangitis (inflamed lymphatic vessels), lymphedema (abnormal accumulation of lymph fluid in the tissues), elephantiasis (disfiguring swollen of limbs), and hydrocele in males.

According to WHO data, about 120 million people in the tropical and sub-tropical areas are infected with LF.

Globally, about 73 countries are endemic and 1.39 million people at risk require preventive chemotherapy. South-East Asia and Africa are the most affected regions. WHO reports that among the 73 endemic countries, 68 have completed mapping their endemic foci, 11 countries have made progress and 2 have yet to start the process (73).

Figure 1.3 Global distribution and status of delivering PC for LF, 2013.



(74).

China and the Republic of Korea were declared to have eliminated LF as a public health problem in 2007 and 2008, respectively.

The GPELF is a PPPs established in 2000 between GSK and WHO, for the donation of albendazole free of charge for as long as needed to eliminate LF as a public health problem in endemic area by 2020. Albendazole represents the gold standard for the treatment of LF, in combination with diethylcarbamazine citrate (DEC) or in combination with ivermectin in area where LF is co-endemic with onchocerciasis.

The governance of GPELF is composed by WHO, the Technical Advisory Group (TAG) established by WHO to provide expert advice to the GPELF, and the LF Programme Review Group (PRG) to monitor the country progress and to

address specific technical issues; in 2002 the PRG was decentralized to the LF Regional programme review Group (RPRG). The Global Alliance to Eliminate Lymphatic Filariasis (GAELF) was established in 2000 supporting and assisting the GPELF in advocacy, mobilizing resources and coordinating partners. *(75)*.

The primary goals of the programme are:

- The eradication of LF as a public health problem by 2020, through the MDA interrupting the transmission;
- The control of morbidity, alleviating and preventing the suffering of people affected by the disease.

The MDA aims to treat the entire population at risk for a period long enough to ensure that the levels of microfilariae in the blood remain below those necessary to sustain transmission. To attain the first goal, four main strategies have been defined:

- Map the geographical distribution of the disease;
- Implement mass drug administration (MDA) annually for 5 years;
- Implement surveillance post MDA;
- Verify the elimination of transmission.

(76).

In addition, WHO developed four steps to follow in order to interrupt transmission:

- Areas suspected of being endemic are mapped to determine the geographical distribution of the disease and identify area where MDA have to be implement;
- MDA is implemented and continued for at least 5 years to reduce the number of parasites in the blood to levels that will prevent mosquito vectors from transmitting infection;

- Surveillance is implemented after MDA is discontinued to identify areas of ongoing transmission or recrudescence;
- If criteria are met, the elimination of the disease is verified (3).

Mapping the disease is of primary importance to know the area to treat and distribute the drug. Determining the presence of LF is easy to do through Rapid Immunochromatographic Card test (ICT). It is a rapid, highly sensitive and specific finger prick test blood for *W. bancrofti* circulating Og4C3 antigen, used as community serologic surveys, to determine the target areas for MDA *(77)*. The relative expensive cost represents the only disadvantage, costing US$1.50, so the surveys are made in the geographic scope *(78,79)*.

Also for GPELF, MDA is the elected method for the distribution of albendazole, as part of the PC global strategy, reaching all eligible people in endemic areas where the prevalence of LF is greater than 1% *(78)*. The aim of MDA is the reduction of microfilaria prevalence and density in the blood. The regimens recommended by WHO are:

- Once-yearly treatment with a single dose of two medicines co-administered, albendazole 400 mg plus either ivermectin (150-200 μg/kg) or albendazole plus DEC (6mg/kg) for a period of 4-6 years, because this period corresponds to the estimated reproductive life span cycle of adult worms;
- Exclusive use of table and cooking salt fortified with DEC for a period of 1-2 years. This latter regimen has led to the successful elimination in China, representing a challenge to implement and expand in other settings

LF is co-endemic with Loiasis in nine countries, impeding MDA in these areas due to the severe adverse reactions that ivermectin causes in presence of loiasis *(79)*. Despite the MDP and ITI implementation strategies principally based on

MDA, GPELF includes both MDA and Vector Control (VC), especially in co-endemic areas where ivermectin cannot be used. VC is feasible and plays an important complementary rule both in the MDA and post-MDA surveillance phase *(80)*.

Different kinds of strategies have been implemented to reach target populations including door-to-door distribution or delivery through fixed post, schools, workplaces and other central points. The CDT strategy is the strategy of choice also for LF, called Community Directed treatment with ivermectin plus Albendazole (CDTI+). Normally community volunteers perform it after they have taken a "village census" and training activities *(81)*.

MDA has been implemented in 60 countries, of which 15 have reduced infection prevalence, stopped MDA and started surveillance. 22 countries achieved the 100% geographical coverage, conducting MDA in all endemic areas of the country, and 23 are conducting MDA but without covering all endemic areas. Since 2000, a cumulative total of 4.9 billion doses of medicines have been delivered to 1 billion people *(82)*. WHO also reported that during 2013, the programme targeted 563.5 million people through PC and treated around 410 million people, accounting for 72.8 of coverage (83*)*.

An estimated 19.5 million preschool-aged children between 2 and 4 years of age, and 101 million school-aged children between 5 and 14 years of age were treated globally. In order to verify the MDA state, sentinel and spot check site surveys are routinely conducted to monitor and evaluate the population reached, and also to determine if MDA can be stopped and post-MDA surveillance can start. Transmission assessment survey (TAS) is a new tool used for 6-7 year old children to guide programme manager decision-making in order to stop MDA. A programme area, the Implementation Unit (IU) is considered eligible for TAS when all of the following criteria are met: (i) at least five rounds of MDA have

been implemented; (ii) coverage exceeds 65% of the total population in the IU for each of five rounds of MDA; and (iii) the prevalence of infection in sentinel and spot-check sites is below 1% (assessing microfilaremia) or below 2% (assessing antigenemia, usually by ICT test). Once an area passes the TAS requirements, post-MDA surveillance begins *(80)*.

Over the first 8 years, it has been calculated that more than 6 million cases of hydrocele and 4 million cases of lymphedema were prevented, and about 32 million DALYs averted *(84)*.

The effective strategy to tackle LF resides in the implementation of MDA and in the control of morbidity of people already affected, including lymphedema, elephantiasis, or hydrocele. The control of morbidity aimed to reduce the burden of disease and preventing disability *(81)*.

Another study estimated the cost of MDA for LF across 7 countries: Burkina Faso, Ghana, Egypt, Tanzania, the Philippines, the Dominican Republic, and Haiti. The cost analysis protocol was designed to estimate the total annual cost of the national MDA program cost for LF including training, mapping, mobilization, distribution, monitoring, and surveillance, the average cost per person treated, and the relative contributions of the endemic countries and the external partners. The study includes both economic costs per person treated (all resources used in the program, including donated materials and drugs) and financial costs per person treated (the actual cash disbursements for a program including resources provided by the national government and local communities but excluding the donated materials). The study adopted the national programme perspective, so including both direct and indirect costs due to LF, beginning from the year 2000, calculating the costs in local currencies and converted in US dollars for the final analysis. This study shows that the financial costs per person treated (financial costs include all costs except

donated materials) ranged from US$ 0.06 to US$ 2.23 while economic costs (that is financial cost plus the value of donated materials) varied between US$ 0.40 and US$ 5.8. MDA coverage ranged from 53% to 91%. It has been calculated that the average delivery cost of MDA per person in Haiti is US$0.44; but taking into consideration the drug donation and purchases, the average cost per person increase to US$0.68. The most substantial cost components included per diem (35% of total economic costs), supplies (14% of total economic costs) and personnel (7% of total economic costs) *(85)*.

A study conducted by Remme, estimated the cost of intervention for the elimination of LF, onchocerciasis and Chagas disease and leprosy. In the case of LF they evaluated cost assuming three different scenarios about the MDA duration: 6 years, 10 years, and 30 years. The MDA cost US$4-8 per DALY averted for the first and second scenario and US$29 if MDA continued for 30 years (47, 86).

A meta-analysis conducted by *Chu et al* in 2010, investigated the benefits gained from the GPELF interventions in economic terms, including the direct treatment costs, indirect costs of lost-labour, and costs of health system to care affected individuals. The population taken into account for this economic study is divided into two groups: those protected from acquiring infection, and subsequent disease; those already infected but protected from disease progression. These two groups are segmented into four sub-populations, constituting the "benefit cohort population". According to this study, an estimated US$21.8 billion of direct economic benefits will be gained over the lifetime of 31.4 million individual treated during the first 8 years of GPELF activities. It was calculated that 94% of these benefits result from preventing the indirect costs in terms of lost of working time, and US$2.2 billion will be saved by national health systems as a result of fewer LF infections resulting in

reduction in the cost of providing services to patients (direct costs). Direct treatment costs refer to medicines, consultation fees, transport, food, accommodation; indirect labour costs refer to income lost as a result of reduced hours and economic activity due to LF morbidity.

The ERR of return of GPELF is considered high, estimated to be between $20 and $30 per individual for every $1 invested, recognizing this programme a cost-effective investment for health system *(84)*.

The cost of MDA to treat the entire at risk population for 5-7 years in areas where prevalence in >1% has been calculated in the Conteh et al study, estimated to be $5-10 cost per DALY averted to interrupt transmission and achieve elimination of public health problem *(46)*.

2. Outline of the thesis

The aim of the thesis is to explore the most important DDPs established so far and to conduct an impact assessment of their implementation: MDP founded by Merck & Co. in 1987 for tackling onchocerciasis through the donation of ivermectin; the ITI established to overcome blinding trachoma through the donation of azithromycin thanks to the PPP established in 1998 between Pfizer Inc. and the Edna McConnell Clark Foundation; the GPELF to combat LF through the donation of albendazole, founded in 2000 by GSK and WHO.

The choice of framework on which the impact assessment was based, derives from a retrospective analysis of the available literature, topics and data mostly used to describe the NTDs and DDPs impact. These qualitative and quantitative data were categorized into three major dimensions that cover health, organizational and economic aspects. The literature analysis led to gathering information about the NTDs characteristics and burden, DDPs health achievements and economic analyses. However, due to the differences on study frameworks, criteria of analysis adopted, and variability about data available it was not possible to build a direct comparative analysis of the three DDPs included.

For the health impact the widely parameters used are: diseases endemicity; morbidity and mortality; number of people treated with MDA; total amount of treatments donated; reduction of disease prevalence; number of DALY; number

of DALY averted. These data were mostly derived from DDPs and WHO website and reports.

The economic impact analysis include: the economic burden of the disease, principally in terms of productivity loss; programmes expenditures, including implementation cost, MDA, and treatment costs; cost per DALY; cost per DALY averted; cost per person treated; cost benefits in terms of economic gains and reduction expenditure thanks to the reduction of disease prevalence.

Even though programmes were carried-out with different implementation strategies and developed specific management tools, reviewing the literature some activities commonly developed by DDPs emerged: drug delivery strategies; tools for mapping disease distribution; eligible population inclusion criteria; governance at central and local level. These dimensions are included in order to describe organizational impact and programme management. In addition, qualitative evaluation studies based on semi-structured interviews were conducted for ITI and MDP. For MDP two different studies, evaluating the CDTI sustainability and governance management were conducted. The qualitative study about ITI assessed its activities implementation and sustainability.

Comparing the aspects described above, limits and strengths of programmes and studies conducted emerged, building a critical analysis of DDPs analyzed.

The literature research conducted on PubMed includes articles in the English language published between 1994 and 2014. Keywords used in the research included: “neglected tropical diseases”, “NTDs”, “Mectizan Donation Programme”, “MDP”, “Global Programme to Eliminate Lymphatic Filariasis”, “GPELF”, “International Trachoma Initiative”, “ITI”, “onchocerciasis”, “trachoma”, “lymphatic filariasis”. These were used separately or in combination with the following keywords: “epidemiology”, “economic burden”, “impact assessment(s)”, “achievement(s)”, “health achievement(s)”,

"cost(s)", "DALYs", "cost per DALYs", "cost effectiveness". Exclusion criteria for literature selection were not adopted. Grey literature from Google, WHO and drug donation programmes official websites and reports were also reviewed.

3. Education and research on drug market access in low-income countries: the experience of Department of Pharmaceutical Science in Novara.

Jommi C, Di Procolo P, Drago V, Egea, Milano, pages 129-151, 2013

3.1. Impact evaluation of drug donation programs for neglected diseases

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Introduction

The PhD research project is focused on DDPs for NDs. These programs are usually implemented within a public-private partnership (PPP) framework.

Under the umbrella of a PPP, a variety of collaborations are developed, often with huge differences regarding objectives, governance structure, stakeholders' involvement, and operations. The objectives of a PPP could be:

- The development of new products for ND (e.g. Medicine for Malaria Venture (MMV), the International AIDS Vaccine Initiative, and the Global Alliance for TB Drug Development) (1).
- The donation or subsidizing a product to control a specific disease;
- The improvement of products quality or regulation;
- Strengthening health services.

Disease-specific donation programs built on a PPP in a long-term commitment are recognized as the most effective approach to deliver drugs (1). The first PPP

was the Mectizan Donation Program (MDP), established by Merck & Co. in 1987 and concluded in 2003, and donated ivermectin (Mectizan) for the control of onchocerciasis "wherever is needed, for as long as needed" (2). Other remarkable examples of PPP are the International Trachoma Initiative (ITI) founded by Pfizer Inc. and the Edna McConnell Clark Foundation in 1998 in which Pfizer provided azithromycin (Zithromax) as part of a wider program to eliminate trachoma, and the Global Program to Eliminate Lymphatic Filariasis (GPELF) established in 1998 by GlaxoSmithKline and the WHO, in collaboration with Merck, which donated albendazole (Albenza) with either diethylcarbamazine (DEC) or ivermectin (3). DDPs are focused on delivering drugs, but they usually pursue broader objectives, including administration and distribution systems, training, health education, and monitoring activities (4).

The current PhD project aims at (i) reviewing the literature on impact assessment of the three above-mentioned DDPs (MDP, ITI, and GPELF) (ii) scrutinizing the impact of a project (SMS for Life, within the Novartis Malaria Initiative project) aimed at improving the access to medicine for NDs in LIC. This section is focused on the first part of the project.

Methods and materials

The impact assessment of DDPs includes three dimensions: health achievements, economic impact, and organizational issues.

The health impact is measured through (i) the final outcome: avoided burden of disease (Disability Adjusted Life Years, DALYs, and number of working days lost), and health expectancy, and (ii) the process outcome: the number of people reached and the number of treatments delivered.

The economic impact may be focused on the costs of the program and the avoided costs thanks to the program, the economic value of benefits, or both

benefits and costs of drugs (cost-effectiveness analysis) and the program (cost-benefit analysis).

The organizational impact usually concerns governance issues of the PPP, disease mapping, drug delivery strategies, the relationships among the actors involved, and activities aimed at supporting local communities.

This review covered the full spectrum of impact analyses, with a focus on the relationships among partners both at international and national levels, the drug delivery strategies, and the evidence on programs cost-benefit.

The literature review was conducted from September 2011 to March 2012. Both peer-reviewed articles (through Medline) and grey literature (DDP websites and WHO reports) were considered. The keywords used to investigate the literature where: Onchocerciasis, Lymphatic filariasis, Trachoma, Ivermectin, Albendazole, Zhitromax, Mectizan, Mectizan Donation Program, International Trachoma Initiative, Global Program to Eliminate Lymphatic Filariasis, Public-Private Partnership for health, Burden of disease, Health impact, Economic evaluation, Cost benefits analysis, Cost-effectiveness analysis, Governance, Community-based treatment, Drug Distribution Strategy.

The Mectizan Donation Program (MDP)

Onchocerciasis, also known as river blindness, is a disfiguring parasitic disease that affects eyes and skin transmitted through the bites of infected black flies. It represents the second highest infection cause of blindness worldwide, being endemic in 35 countries among sub-Saharan Africa, parts of Central and South America and in Yemen. Ivermectin is an anthelmintic agent indicated for the treatment of onchocerciasis and LF where LF is co-endemic with onchocerciasis. There are approximately 37 million people affected by this disease and 99% of the cases are in Africa (5). DALYs attributed to

onchocerciasis in 2004 were about 375,000 in Africa, 1,000 in the Americas and 11,000 in the Eastern Mediterranean (6).

The MDP is a PPP founded in 1987 by Merck and the WHO, the Task Force for Child Survival, the World Bank, the UNICEF and more than 35 non-governmental development organizations (2). The primary aim of the project was the donation of ivermectin for the treatment of onchocerciasis. In 1998, the donation was expanded to include the treatment of lymphatic filariasis (LF) in 28 African countries and in Yemen, where onchocerciasis and LF are co-endemic (7). The program was closed in 2003. In addition to its main purpose as a DDP in the endemic countries, its co-objectives were to provide good medical practices and promote appropriate prescribing behavior.

From an organizational viewpoint, an independent committee (the Mectizan Expert Committee), composed of seven experts in international public health and tropical diseases, and an MDP Secretariat were created at the central level to appropriately coordinate the project. Existing initiatives on onchocerciasis have been incorporated to avoid duplication and distrust from the local communities. In Africa, the Onchocerciasis Control Program (OCP) and the Africa Program for Onchocerciasis Control (APOC) represented the local committees. The OCP was established in 1974 and ended in 2002. The APOC was founded in 1995 and will continue until 2015 and is still carrying out the activities begun by the MDP. As far as the Americas are concerned, the Onchocerciasis Elimination Program for the Americas (OEPA) was integrated into the overall approach. This program, founded in 1990, includes six endemic countries: Brazil, Columbia, Ecuador, Guatemala, Mexico, and Venezuela.

As for drugs delivery strategies a Mass Drug Distribution (MDD), supported by vector control, surveillance, reporting and advocacy activities, has been implemented (8). More specifically, the project started with a passive distribution approach, then moved to a mobile teams strategy ("land rover"),

and finally converged toward Community-Based Treatment (CBT). In addition, disease mapping was performed to estimate communities at risk. Disease mapping has relied on divers tools, including the Rapid Epidemiological Mapping of Onchocerciasis (REMO), the Rapid Epidemiological Assessment (REA), and the Rapid Assessment for Procedure for Loa Loa (RAPLOA). Through this approach, ivermectin was actually distributed to the communities living in the endemic countries. The success of this strategy is indirectly demonstrated by the circumstance that most of the subsequent donation programs have adopted it.

The International Trachoma Initiative (ITI)

Trachoma is a chronic bacterial disease transmitted from human to human that still represents the most common infectious cause of blindness worldwide, despite the fact it is preventable and treatable. Azithromycin represents the first-line antibiotic for the treatment of trachoma, based on a single dose regimen (9, 10). According to the WHO data, about 84 million people, mostly women and children, have active trachoma; around 8 million are visually impaired, 8.2 million people have an advanced stage of the disease, called trichiasis, and 1.3 million are blind from trachoma. Trachoma is endemic in 55 countries and about half of the global burden is concentrated in 5 countries: Ethiopia, India, Nigeria, Sudan, and Uganda. In 2004, Trachoma DALYs were estimated as 1,334,000 worldwide, and 601,000 in Africa (6).

The ITI is a PPP founded in 1998 by the Edna McConnell Clark Foundation and Pfizer Inc. The mission of ITI is to eliminate blinding trachoma by 2020, by adhering to the Alliance for Global Elimination of Trachoma by the year 2020 (GET 2020), a WHO initiative set up in 1998 and supported by ITI (11). Through this partnership, Pfizer committed to donate azithromycin

(Zithromax), the first-line antibiotic for the treatment of trachoma. The ITI is part of a broader mission aimed at tackling trachoma. In particular, it represents the implementation of the component “A” of the "SAFE" strategy, launched by the WHO in 1997, which includes surgery to correct trichiasis, donation of Zithromax, facial cleanliness to prevent disease transmission, and environmental change to increase access to clean water, sanitation, and the control of flies.

The collaboration between the Edna McConnell Clark Foundation and Pfizer began in the 1990s by providing support for pilot studies in Egypt and Zambia to test the effectiveness of Zithromax in children affected by active trachoma. The success of the studies intensified the relationship between Clark Foundation and Pfizer that culminated with the birth of the ITI.

ITI is governed by a Board of Directors, the Trachoma Expert Committee (TEC) and the ITI Secretariat. The TEC is an independent body of seven international experts in the fields of public health, ophthalmology, and blindness prevention. The ITI secretariat supports the TEC activities and the Board of Directors, coordinating technical assistance in program planning, monitoring and evaluating, and manages the application process for ITI support (8; 12).

Like MTD, the ITI has been particularly active in disease mapping and drug delivery strategy. Disease mapping has relied on three different methods: the Trachoma Rapid Assessment (TRA), the Population-based Prevalence Surveys (PBPS) and the Acceptance Sampling Trachoma Rapid Assessment (ASTRA). Despite these increasing efforts to map the true occurrence of trachoma, the prevalence is still rather unclear and very difficult to capture (13). The drug delivery strategy focused on an appropriate management and distribution of Zithromax. The application for drug donation starts nearly eighteen months before the drug arrives to the recipient country and it allows ITI to monitoring

whether there are program gaps and gives the local Minister of Health an opportunity to review their country plans (14). Treatment delivery has relied on WHO guidelines on MDD; according to these, a community should receive mass antibiotic treatment when the prevalence of active trachoma is 10% or more in children aged ≥10 years, and should continue for at least 3 years until the prevalence of TF in children aged 1-9 years is below 5%.

The Global Program to Eliminate Lymphatic Filariasis (GPELF)

LF, also known as elephantiasis, is one of the oldest and most debilitating ND, transmitted to humans through mosquito bites. Although it rarely causes death, it represents a major cause of suffering and disability, leading to painful and disfiguring chronic enlargement of the arms and legs of people, from children to adults (15). LF treatment is based on the administration of an annual, single dose of diethylcarbazine citrate (DEC) or albendazole plus DEC or ivermectin (16). LF is endemic in 83 countries, affecting about 1.3 million people, mainly living in the Southeast Asia Region (67%) and Africa (30%). The WHO estimated 5.9 million DALYs due to LF at global level (3.5 million in Asia, 2.2 million in Africa) (6).

The GPELF was launched in 2000 as a PPP between the WHO and GlaxoSmithKline (GSK). The partnership aims at eradicating LF as a public health problem by 2020 through the donation of albendazole (Albenza) by GSK and alleviating pain and preventing disability caused by LF (17). The GPELF was anticipated by different events that increased the awareness on LF eradication. In 1993, the International Task Force for Disease Eradication included LF in the list of the eradicable or potentially eradicable diseases. In 1997, the World Health Assembly called for countries “to strengthen activities

toward eliminating LF as a public health problem". The formal collaboration between GSK and WHO, by providing albendazole free of charge for as long as needed to eliminate LF, was strengthened by the donation of ivermectin by Merck & Co., a drug also used for the treatment of LF, particularly where it is co-endemic with onchocerciasis.

The governance structure of GPELF is very complex. More than 27 international partners assist and support this PPP. This complexity has driven the founders to create a new PPP (Global Alliance to Eliminate Lymphatic Filariasis, GAELF) in 2000, to manage advocacy, coordinate partners and mobilize resources; this initiative also involved the Minister of Health of the 81 endemic countries, NGOs, and international organizations (17). The WHO and the Technical Advisory Group (TAG) that advices WHO on the relevant key issues, together with the GAELF, are the main components of the GPELF governance. At regional level, the activities are supported by the Global Program Review Group (Global PRG).

Delivery strategies and implementation of the donation program are mainly coordinated by the WHO, with the support of GAELF. Disease mapping, assuring MDD, assessing outcome of the national programs, and surveillance initiatives were the main focus of implementation. Disease mapping has relied on a finger prick rapid blood test, named Rapid Immunochromatographic Card Test (ICT), and used for community serologic (18). An MDD has been carried out for at least 5 years. Door-to-door distribution, distribution through fixed posts and schools, and community-based distribution were implemented, the latter being the most successful. Despite the fact that prevention was another important part of the program and behavioral measures, including the improvement of hygiene habits, are essential to avoid the disease, only 27 countries have active morbidity-management actions (19).

Impact assessment of the three PPPs

The impact assessment of PPP for ND may consider health achievements, organizational impact, and economic impact.

Health achievements can be measured with process outcome or final outcome indicators. Process outcomes include the number of treatments delivered and target population covered. Thanks to MDP more than 1.5 billion ivermectin tablets have been donated, with more than 700 million people treated (20). Pfizer has provided more than 225 million antibiotic treatments for the implementation of the "A" component of the SAFE strategy to eliminate blinding trachoma. In 2006, Morocco announced the elimination of trachoma as a public health problem, followed by Ghana in 2008. Through the GPELF, GSK donated 1 billion tablets of albendazole and Merck donated 780 million ivermectin treatments for LF (6), but the target population covered is still unknown.

As far as the organizational impact is concerned, this impact strongly depends on each PPP's scope. All the relevant diseases are not life threatening and are preventable. Hence, treatment availability and affordability are as important as actions, which aim at improving behavioral and environmental risk factors. In all programs, drug donation has been integrated with other activities. The MDP implemented vector control activities to enhance the disease eradication. The GPELF has been focused on the interruption of the transmission and the management of morbidity, with a special attention to hygiene habits. The ITI program is part of a wider strategy that includes actions aimed at increasing access to safe water and sanitation and initiatives to improve hygiene habits to prevent disease transmission.

Another common feature of the three programs is the central role played by disease mapping and distribution strategies. Whereas the MDP and the GPELF

successfully developed tools for mapping the relevant disease, in the case of trachoma, disease mapping was not good enough to identify appropriately the target population.

Distribution strategies have mostly relied on MDD and CBT. CBT was introduced by the MDP. This approach empowers communities in the endemic countries, giving to them adequate information to get involved in decision-making, organization, and mobilization of resources. Through the CBT, the communities become accountable for delivering the treatment by deciding how, when, and by whom the treatments should be administered. The success of this strategy led to its use for the control of malaria, LF, schistosomiasis, eye care, maternal and child health, nutrition, and immunization in various countries (21). As for trachoma, despite the fact that the delivery strategy has not been sufficiently described, an impact assessment of ITI was carried out by the London School of Hygiene & Tropical Medicine (LSHTM) in eight countries (22). The current research project detected positive achievements (i.e. MDD of high-quality antibiotics) in most countries even in extremely resource-poor settings, with a target population coverage within communities generally exceeding 80%. However, a lack of detailed data of trachoma endemicity and poor monitoring activities of the SAFE were highlighted. In addition, inadequate water and sanitation have remained a major problem.

Whereas all the PPPs considered have created strong governance at the central level, only the MDP implemented an integrated strategy with the involvement of regional organizations. Three independent organizations were integrated into the program: the OEPA in the Americas, the APOC, and the OCP in Africa. The APOC is still working in Africa and represents an important institution for the eradication of onchocerciasis. According to a 2004 survey, the 21 partners involved in the MDP felt satisfied with and perceived benefits from the collaboration with the MDP and also observed a clear separation between

Merck's role in providing and shipping the drug and the Expert Committee and Secretariat's role in providing technical expertise (23).

Different studies have been carried out on the costs and economic benefits of the three PPPs scrutinized. The economic benefits are usually expressed as avoided DALYs by the program.

There are several economic analyses on MDP, even if mainly focused on the first period of the program implementation in Africa and considering APOC and OCP separately. However, the studies show important discrepancies, depending on costs included and the time horizon considered. The WHO estimated an average 850,000 DALYs averted per year thanks to the APOC activities, with a cost of USD 9 per DALY averted (6). Another set of studies measured the value for money of the program in terms of Economic Rate of Return (ERR), the discount rate that sets the net present value of the stream of net benefits equal to zero. A public health program with a 10% ERR is considered successful by the World Bank. The WHO estimated a ERR of 20% for OCP in 1974-2002 and 17% for APOC in 1996-2008. Another set of studies has shown a huge increase in the labor productivity thanks to MDP (23, 24).

The evidence on the economic impact of other programs is poorer than those for MDP. In addition, economic impact assessment of ITI on trachoma suffers from a limited availability of reliable data on the disease sequelae prevalence in the endemic population and the paucity of robust population-based surveys for estimating the number of affected people (25).

The overall economic benefit of the GPELF during the period 2000-2007 is estimated at USD 24 billion, with a cost per DALY averted per person of USD 5.90 (26). The cost of the SAFE strategy for trachoma has been estimated at USD 54 per case of visual impairment prevented (27). The implementation of this strategy cost USD 5 per DALY averted (6). Considering that people with

blindness are supposed to lose 100% productivity, the 2003 economic loss due to trachoma was estimated at USD 5.3 billion (27).

Summary of the evidence on impact assessment

Program	Objective	Partnerships	Disease worldwide prevalence	Drug Delivery Strategy	Health achievements	Cost per DALY averted	Cost per person treated	Cost-benefit
MDP	Donation of ivermectin for the treatment of onchocerciasis	Merck & Co., Task Force for Child Survival, WHO	37 million	Mass Drug Administration through Community-based Treatment	From 1988 to 2008 more than 1.5 billion ivermectin tablet donated	9	0.58	OCP: ERR 20% (1974-2002) APOC: ERR 17% (1996-2008)
ITI	Donation of azithromycin, as part of the SAFE strategy, to eliminate blinding trachoma by 2020	Edna McConnell Clark Foundation, Pfizer Inc.	84 million	Mass Drug Administration for five years	From 1998 more than 225 million antibiotic treatments donated	5	0.50	Not available
GPELF	Donation pf albendazole with either diethylcarbamazine or ivermectin for Lymphatic Filariasis, and eradication of Lymphatic Filariasis by 2020	WHO, GSK, Merck & Co.	120 million	Mass Drug Administration for five years through Community-based Treatment	From 2008 1 billion tablets albendazole 781 million ivermectin tablets donated 32 millions DALYs averted since 2000	5.90	0.45	Net economic benefit: US$24 billion (2000-2007)

The literature review on the impact assessment of DDPs carried out by a PPP has shown important achievements, even if some results are controversial, especially for ITI program for trachoma. Despite the fact that health achievements and the economic impacts are most important targets of these programs, the literature stressed the relevance of the governance structure and delivery strategy. Long-term sustainable control of NDs through active PPP requires a huge commitment from all partners involved, integration between central governance and regional institutions, and an accurate definition of the delivery strategy with MDD and CBT as the pillars of this strategy.

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4. Conclusion

The PPPs analyzed differ in the strategies and governance they have adopted, the stakeholders involved and population reached. However, being a vertical programme, MDP, ITI and GPELF aim to focus on the control and elimination of a single disease through the long-term commitment of pharmaceutical companies, and have established common activities through which it has been possible to reduce the social and economic burden of the diseases *(27)*. The attention of international stakeholders has grown even more in recent years, due to three greatly influencing features of NTDs: they are poverty-promoting; there are low-cost and highly cost-effective control approaches that might eliminate some of the diseases and create universal access to essential medicines; moreover, the full control of these diseases would have simultaneous and sustainable effects on poverty reduction (87).

4.1. Health and organizational impact

The analysed PPPs, along with drug donation have adopted managing, reporting, advocating and surveillance activities projected on the base of disease features *(33, 77)*. The MDP, along with drug donation, has implemented vector

control activities in OCP areas for enhancing the eradication of the disease, it has also established CDTI, training of CDD, and monitoring activities *(32)*.

The GPELF has two aims: to interrupt the disease transmission and manage disease morbidity. One of the key elements that might contribute to the successful elimination of LF by 2020 is the ability of the treatment to not only reduce disease morbidity, but also halt the progression of early subclinical disease in those already infected *(2)*.

ITI is focused on delivering the antibiotics needed, thus implementing the "A" (i.e. antibiotics) component of the SAFE strategy.

Thanks to MDP more than 1.5 billion ivermectin tablets have been donated *(88)*. Pfizer has provided about 340 million antibiotic treatments for the implementation of the "A" component as part of the SAFE strategy and, as a result of this donation, in 2006 Morocco was the first country that announced the elimination of trachoma as a public health problem, while Gambia and Ghana are still in the post-endemic surveillance stage *(63, 64)*. Through the GPELF, a cumulative average of 4.9 billion treatment doses have been donated *(82)*. It has been estimated that thanks to GPELF more than 32 million DALYs have been averted *(89),* while in the APOC areas about 8.2 million DALYs, between the period 1995-2010 have been averted *(44)*.

Due to the nature of the programmes, managed by international bodies and addressing health problem affecting poor people, who mostly live in remote areas of Africa, it was of primary importance to build intertwined governance between central and local levels. All of the DDPs analyzed have well-defined governance, where each body involved has a specified role and responsibilities, as shown in table 4.1. Among the three programmes analyzed, MDP governance is based on local organizations (OCP, APOC, and OEPA) that operate independently.

Table 4.1 DDPs governance, objective and partnerships.

Programme	Objective	**Medicine donated**	Governance	Partnerships
MDP	Control and elimination of onchocerciasis	Ivermectin	Mectizan Expert Committee, MDP Secretariat, OCP, APOC, OEPA	Merck &co., WHO, the Task force for Child Survival ad Development, UNICEF, more than 35 NGOs, World Bank, WHO
ITI	Elimination of blinding trachoma by 2020	Azithromycin	ITI Board of Directors, TEC, ITI Secretariat	Pfizer Inc. Edna McConnell Clark Foundation, WHO and other international organizations, NGOs, local institutions
GPELF	Elimination of LF by 2020	Albendazole	WHO, TAG, GAELF, Global PRG	WHO and other international organisations, GSK, Merck & Co.

Qualitative evaluations of programme management were carried out for MDP and ITI, but so far, there has been no qualitative assessment of GPELF activities. Two different evaluations were, however, performed for MDP, assessing CDTI sustainability on one side, and governance and partnership management on the other.

Results from studies exploring CDTI performances show that at community level, over 70% of projects were positively perceived *(51)*.

In 2004 Burnham and Mebrathu conducted a study based on semi-structured interviews of staff, analyzing the institutional relationships among the bodies

involved. The results showed a positive perception of collaboration between local and international bodies. The clear separation between the stakeholders is perceived as a contributing factor for programme success. The major issues raised regard record gaps among the APOC communities and monitoring activities at OCP level *(33)*.

ITI has also undertaken a qualitative evaluation of its activities. Not only successful achievements emerged, but also key issues, including a lack of detailed data about trachoma endemicity. This lack of data represents one of the major obstacles to programme planning, seen as a poor monitoring activity of the SAFE strategy. Furthermore, despite the efforts made, inadequate water and sanitation remain a major problem in all programme areas *(71)*.

MDP, ITI and GPELF have successfully implemented PC, which is also being used in the case of schistosomiasis and soil-transmitted helminthiasis, thus ensuring a high level of coverage. PC inclusion criteria were based on the disease features, and a specific tool for the disease detection was developed, as described in table 4.2.

Table 4.2 MDA features and diseases burden.

Disease	Clinical manifestation	Endemicity	MDA inclusion criteria	MDA population
Onchocerciasis	OSD, visual impairment, blindness	37 countries	Nodule prevalence ≥ 20%	MDA to total eligible population* in hyper-endemic and meso-endemic areas
LF	Adenolymphangitis lymphedema, hydrocele	73 countries	Prevalence of LF is greater than 1%	MDA to total eligible people in endemic areas
Trachoma	Trachomatous folliculitis and inflammation, trichiasis, visual impairment, blindness	51 countries	Prevalence of active trachoma is ≥ 10%	MDA to total eligible people in endemic areas

*the following are not eligible: pregnant women and children weighting <15 kg

Among the various methods used to implement drug delivery strategies, CDT seems to be the most cost effective distribution method. CDT was originally introduced by APOC for the distribution of ivermectin and subsequently used by other DDPs for the control of LF and malaria; however, it has not been clearly recognized for the control of trachoma. CDT represents one of the most important interventions used to fight NTDs, being sustainable, highly cost-effective and feasible. Its cost effectiveness has been reported in different studies.

In a three-year multi-country study APOC assessed the sustainability of community directed intervention (CDI) from 2005, to understand if CDI could be used to fight other diseases in communities with prior CDTI experience. The study showed that the CDI approach was more effective than the one currently used for all cases analysed, including malaria treatment, distribution of

insecticide-treated nets (ITN) for malaria prevention, vitamin A supplementation, ivermectin for onchocerciasis, except for short course directly-observed treatment of tuberculosis (DOTS). Moreover, without any increase in implementation costs, the CDI process achieved higher coverage for different interventions *(90)*

Other interesting evidence derived from a study conducted in Ghana to assess the role of CDT in achieving a higher coverage rate for LF elimination. The study showed that the various communities and health staff appreciated the fact that CDT was much more involved in regular public-health services at implementation level (ComDT/HS) than the mass treatment in which only the health services participated (HST). The treatment coverage achieved by ComDT/HS was much higher (74.5%) than that of the health system (HST) (43.5%) *(91)*.

Willingness to pay (WTP) gives a comprehensive insight into how people value a health intervention. WTP studies analyzed gave mixed results. For example, one such study investigating the WTP for prevention and treatment of LF in Haiti shows that, although most of the community placed a positive value on both of these aspects, 7% of households were not willing to pay for prevention while 39% were unwilling to pay for treatment, therefore, any cost recovery policy would probably result in inadequate participation and limited sustainability *(92)*.

A baseline survey carried out in two villages in Nigeria showed that 93.3% and 92.6% of the households in Achi and Nike, respectively, were willing to pay for ivermectin distribution, with the mean willingness to pay per dose equaling $0.30 in Achi and $0.28 in Nike. As the level of willingness to pay reaches the cost of programme implementation, a sustainable programme becomes increasingly feasible *(48)*.

An important aspect that enforces the sustainability of CDT strategy is the ability to involve local communities. This involvement could lead to an increased awareness of the disease, encouraging the communities to take a greater interest in making decisions, which would, in turn, help them to feel more responsible and understand how important it is to get treatment.

CDT is focused on encouraging communities to take responsibility for drug delivery, deciding how, when and by whom the treatment should be administered, as well as choosing their CDDs *(38)*. Moreover, the people directly involved in CDTI are usually volunteers, often involved in other health interventions, which contributes to the cost-effectiveness of this type of strategy *(21)*.

An important parameter commonly used for weighting the burden of NTDs is DALY, whose available data are often uncertain, not up-dated and incongruent. This can be explained by the fact that the estimation of DALYs is a sum of different elements, including the amount of population affected, population treated and the burden of the disease, in terms of number of people dying from the disease or living with the disability. According to Burton these data are not always easy to estimate (93).

The number of DALYs reported by different authors is taken from the Global Health Reports and calculations are made by WHO. All papers report the number of DALYs calculated in the Global Health Report 2004 *(94)*.

Table 4.3 DALYs referred to Global Health Report, 2004.

Diseases	DALY 2004*	DALY up-date **2004
Onchocerciasis	484,000	389,000
LF	5,800,000	5,941,000
Trachoma	2,300,000	1,334,000

*according to WHO Health Report, 2004. http://www.who.int/whr/2004/en/

**WHO Library Cataloguing-in-Publication Data The global burden of disease: 2004 update. World Health Organization, 2008. 2004 data updated in 2008.

These data have been up-dated in 2008: with calculations of YLL and YLD using an additional 3% of time discounting, and non-uniform age weights that give less weight to years lived at younger and older ages. A complete update was undertaken for estimated deaths by age, sex and cause for all WHO Member States. There were 192 Member States in 2004 *(95)*.

The latest DALYs published by WHO refer to the year 2010 *(96)* as showed in table 4.4. However, because these estimates draw on the results of the Global Burden of Disease (GBD) 2010 study, the estimates for the years 2000-2011 are not directly comparable with the previous WHO estimates of DALYs for the year 2004 or earlier. A simple form of DALY used by the GBD of 2010 study has been adopted; age weighting and time discounting are dropped; the YLDs are calculated from prevalence estimates rather than incidence estimates, and YLDs are also adjusted for independent comorbidity. The standard life table used to calculate the years of life lost due to death at a given age is based on the projected frontier life expectancy for 2050, with life expectancy of 92 years at birth. Differences between these estimates and those previously published by the WHO should not be interpreted as representing time trends because

estimates from earlier years are not generally comparable due to changes in methods and data. In particular, the main DALY estimates published by WHO in the past, incorporated age-weighting and time discounting (97).

Table 4.4 DALY, according to the Global Health Report, 2000- 2011.

Diseases	DALY 2000	DALY 2011
Onchocerciasis	604,000	564,000
LF	2,547,000	2,740,000
Trachoma	426,000	308,000

4.2. Economic impact

As regards the economic evaluations, there is a general lack of standardization in the presentation of cost estimates; the inclusion criteria are not standardized; many studies do not adequately specify the time period during which data were collected, whether the costs were economic or financial; nor do they define the year and currency in which results are presented. Due to these methodological caveats, direct comparison among studies is challenging. Much of the literature about control and treatment costs for these diseases is dated, especially in the case of MDP, limiting the possibility to compare costs and cost-effectiveness for the different interventions and studies *(98)*.

Most of the economic studies scrutinised used the loss of productivity due to the disease (especially due to disease morbidity rather than mortality) as a

parameter to calculate the economic burden of diseases, and the majority of studies calculating the economic costs of the programs did not include drug costs. The economic value of a programme have been mainly evaluated through cost per DALY averted.

Referring to MDP, several studies have evaluated the cost of MDA either as part of OCP activities or as part of the APOC activities, with the CDTI costs and cost per DALYs averted *(34, 42, 44-47)*. Studies regarding the cost of MDA based on CDTI for onchocerciasis vary significantly, ranging from a financial cost of US$0.20 per person in Nigeria *(48),* to a MDA cost through CDTI in Uganda estimated to be between US$0.13 to US$1.20 across the district *(38)*. The main driver of this variation was thought to be the size of the population, suggesting that there may be economies of scale when CDTI is conducted in more heavily populated areas. It has been estimated that the cost of treatment decreases when it is distributed through the CDTI and when it is associated with LF, schistosomiasis and soil transmitted helminth infection. This can be explained assuming that both economies of scope and scale coexist with co-administration and when addressed to a wider population *(98)*.

Coffeng estimated a total 8.2 million DALYs averted at a cost of US$257 million thanks to APOC activities, in a time frame of 15 years (1995-2010). He estimated the MDA cost per DALY averted at US$31, considering the programme to be highly cost-effective *(44)*. Remme, considering the same time frame of 15 years within the APOC areas, calculated the total MDA cost through CDTI at US$209 million *(45)*. The CDTI cost per DALY averted has been assessed by several authors, giving variable results: Remme calculated it at US$7, Conteh $9, and Laxminarayan at US$6 per DALY averted (*45-47)*. Turner estimated a total amount of $41,536 the annual cost of CDTI for 100,000 people, considering the intervention highly cost-effective *(34)*. Waters

in 2004 defined the ivermectin distribution cost per DALY prevented at $14-30 *(42)*. Coffeng reports treatment cost at US$0.51, and WHO assessed the cost per person treated with ivermectin at $0.57, yielding an ERR at 17% *(44)*. A result comparable with that obtained from the studies conducted by Kim and Benton in 1995 that calculated an ERR of 18% over a time horizon of 39 years *(43)*. The average cost per person treated, including volunteer's time reported by Basanez is $0.74 per person *(99)*.

Onwujekwe reports treatment cost at $0.17 and $0.13 per dose in two villages in Nigeria. This estimate includes the direct financial costs, opportunity costs, advocacy, mobilizing the community, training and distribution *(48)*.

It is important to highlight that the donation of drugs at no cost is the main factor that makes this a highly cost effective intervention. A sensitivity analysis conducted by Waters et al. indicated that including the drugs donated by Merck in only one year, valued at market prices, would outweigh the economic benefits of the OCP and APOC programs over their lifetimes. In fact, if the cost of ivermectin was calculated at $1.50 per tablet (it is the unit value of ivermectin production cited by the MDP) the economic evaluations would not be positive *(42)*.

The amount of ivermectin donated up to 2010 represents a value of US$2.1 billion, assuming 2.8 tablets per treatment and a commercial price per tablet of US$1.50 plus US$0.005 shipping costs (personal communication with Dr. A.Hopkins, director of the Mectizan Donation Program). This amount is eight times the program costs for coordinating mass treatment. Likewise, the value of donated ivermectin for the period 2011–2015, should be an additional US$1.8 billion. Therefore, mass treatment with ivermectin can only be sustained if, as Merck has pledged to do, donations of ivermectin continue for as long as necessary *(43)*.

The same consideration can be made for LF; it has been calculated that the average delivery cost of MDA per person in Haiti is of US$0.44; but taking into consideration the drug donation and purchases, the average cost per person increases to US$0.68 *(100)*.

The economic value of GPELF was investigated by Goldman in two different studies: in the study conducted in Haiti he estimated that the MDA delivery costs at US$0.44 *(100);* while in a multi-country study he assessed the financial cost per person treated ranging from $0.06 to $2.23, with an economic cost ranging from $0.40 to $5.87*(85)*. The main factors that affect the cost variations are (i) the aging of MDA programs: in fact MDA program start-up year resulted in higher financial and economic costs per person treated; (ii) the size of population to treat: once the size of the population increases, the treatment cost drops; (iii) the use of volunteers that has the greatest impact on costs. The results of this study highlighted that MDA for LF can be considered inexpensive compared with the other public health programs. Governments and communities represent the major financial contributor for the implementation of MDA *(85)*.

Remme assessed that the cost per DALY averted by using MDA for LF treatment varied depending on the duration of MDA, from $4 per DALY averted in 6 years, to $8 if MDA lasts for 10 years, and $29 in 30 years of activity *(86)*. These results show that the annual MDA to treat the entire "at risk" population (for a period long enough to interrupt transmission) is US$4 to $8 per DALY averted which can be considered a cost-effective approach for eliminating LF in high priority areas. The meta analysis of Chu about the first 8 years of GPELF activities calculated $21.8 billion of direct economic benefits gained over the lifetime considering 31.4 million individuals treated, with an ERR of $20-$30 per $1 invested *(84)*.

The economic studies of trachoma and SAFE strategy are not numerically substantial and do not specify which kinds of costs are included. The study conducted by Evans assumed a cost of $47 per case of visual impairment prevented, excluding the cost of surgery; this predated the introduction of SAFE strategy so it cannot be considered for ITI economic impact assessment. Conteh's estimation varies significantly, with costs ranging from $5 to $100 per DALY averted, due to the fact that all SAFE activities are included *(46)*.

Frick assessed the burden of trachoma in two different studies: in the first it calculated it at $2.9 billion in lost productivity, rising to $5.3 billion in the latest study, considering the productivity lost from blindness to be 100% instead of 60% *(70)*.

Several economic studies are focused on the impact of surgery for trichiasis resulting in a cost-effective intervention, but this aspect lies outside the object of ITI activities *(101, 102)*.

The economic burden of diseases analyzed depends mostly on the indirect cost deriving from lost productivity due to the diseases. In fact, these diseases have an important burden in terms of disability, even if all of them are preventable and rarely cause death. The impact of onchocerciasis includes lost economic productivity, diminished earnings; adverse effects on the labor demand and reduced agricultural output. Thanks to the efforts made by the APOC and OCP, literature reports an increasing number of productivity labor *(103)*.

Kim and Benton calculated that the OCP activities improved health among the adult population, and thanks to the additional onchocerciasis-free situation agricultural and labor productivity have increased generating an estimated $3.7 billion *(45)*.

LF rarely causes death, having a huge impact in terms of disability due to painful swelling and hydrocele commonly associated with an advanced

infection status *(98)*. Blindness in rural Africa has previously been assumed to result in an annual productivity loss of US$150 per case. Likewise, the productivity loss due to itchiness among coffee plantation workers in an Ethiopian site has been estimated at around US$5.32 per month per case *(44)*.

Cost effectiveness analysis supports priority setting by defining areas of action where the greatest health gains can be achieved. In order to define whether or not an intervention is cost effective, the WHO, in 1998, developed the CHOICE initiative (CHOosing Interventions that are Cost-Effective), with the objective of providing policy makers with evidence to help them decide on introducing interventions and programmes, which would maximize health with the resources available *(104)*. WHO-CHOICE has developed threshold values for incremental cost-effectiveness ratio of an intervention. Threshold values are calculated in dollars referring to the year 2005, using GDP, deriving three categories of cost-effectiveness:

- Highly cost effective (less than per capita GDP);
- Cost effective (between one and three times per capita GDP);
- No cost-effective (more than three times per capita GDP).

The World Bank arbitrarily established another evaluation criteria, defined a health intervention that costs less than US$100 per year of life saved as highly-cost effective for poor countries. Moreover an ERR of 10% was considered by the World Bank as a standard for successful public health programmes.

According to these parameters Molyneux affirmed that controlling NTDs is a cost effective strategy, with an annual ERR ranging from 14-30% (*105)*. The low cost of treatment per DALY averted, and the affordable total costs required for the implementation of the DDPs contribute to the programmes affordability.

It has been reported that DALYs calculation can lead to a total DALY burden that might be underestimated, leading to an unrealistic estimation of cost-effectiveness *(18, 46)*.

The studies about the burden of trachoma have several weaknesses. First, the limited supply of reliable data on the prevalence of disease sequelae in the endemic population. Secondly, there are relatively few robust population-based surveys that can be used to estimate the number of people affected *(93)*.

The estimates of cost and the benefits of onchocerciasis control did not include the effect on OSD. Hence, these rates underestimate the benefits, because itching is a severe morbidity caused by onchocerciasis that accounts for more than 50% of the DALYs attributable to onchocerciasis *(106)*.

Conteh argues that DALYs might not adequately indicate the severity of many neglected tropical diseases and the effect on an individual's quality of life and subsequent DALY scores. For example APOC treats only hyper-endemic and meso-endemic communities; hence, the number of infected individuals in hypo-endemic communities (i.e. <40% prevalence of infection), and the burden of eye and skin disease in those areas is not known. Many populations in the poorest areas are also polyparasitized, a phenomenon not previously assessed in terms of disease-burden calculations *(46)*.

The treatment donated for onchocerciasis, trachoma and LF account for an average $0.46 per person treated, considering also the long-term period of operation *(107)*.

Some estimates show that NTDs in sub-Saharan Africa can be treated at a rate of $0.40 to $0.79 per patient, accounting for a total $204 million per year on the continent *(108, 109)*.

The costs for treating NTDs are much lower than treatment costs for HIV/AIDS, malaria and tuberculosis. Comparing the treatment cost of NTDs

estimated to be an average of $0.50 per person per year, to those for HIV/AIDS that can exceed $700 per person per year, and compared to the estimated $6.64 to treat one case of malaria, it appears evident that addressing NTDs is extremely cost effective *(15)*. These affordable costs depend on important factors: the drugs are donated free of charge; the use of volunteers, especially at local level, who are often not paid; the possibility of synergizing delivery treatments *(46)*. The DDPs have been positively influenced from the economies of scale, because increasing the size of a programme up to a defined threshold reduces the average unit cost. Also the economies of scope play an important role in the efficiency of programmes. In fact, when a strategy can be associated and implemented along with others addressing the same population *(110, 111)*.

MDA integration is possible due to the overlapping of disease prevalence in most African countries that can lead to a reduction in costs, and the optimal use of scarce resources. The possibility to implement MDA with the distribution of just four treatments through six PPPs, which are able to combat seven of most debilitating NTDs, has been recognized as feasible and affordable. It has been estimated that for US$200 million annually, approximately 500 million Africans could be treated in a four-drug integrated pro-poor package, at US$0.40 per patient. Cost saving including delivery could reach an estimated 25%, and can be combined with vaccinations and vitamin A supplies *(107, 109)*.

A study conducted in four districts in Niger compared the cost of an integrated PC to control trachoma, schistosomiasis, LF and STH with the cost of a vertical PC control. Leslie shows that the average economic cost of an integrated PC was US$0.197/treatment excluding drugs, and the financial cost was US$0.09/treatment. The average cost of a vertical programme was US$0.167 for trachoma, US$0.10 for schistosomiasis and STH and US$0.075 for LF.

Results suggested that integrated programmes had savings of 16% and 21% in programme costs in 2008 and 2009, respectively, compared with vertical programmes *(112)*.

This integrated control has led to an optimal use of resources, reducing treatment costs and highlighting logistic convenience. The benefits reside also at health level, because integration improves the compliance of people affected thanks to the integration of administrations, and can also reduce drug resistance *(12, 15, 57, 110)*.

The efforts made by the PPPs established for NTDs, and the increased interest at international level, is having a huge positive impact for the million people affected and living in LICs, *(21)*. However, despite the efforts to improve health access through a vertical programme, health achievements have not improved as much as expected because of weak healthcare systems. Even though integrating intervention might be a cost effective approach in co-endemic countries, the fragile health system represents an obstacle for its inception *(113)*.

In the future, the concept of integration could have a broader application rather than the PC control, including access to clean water and sanitation; strengthening surveillance, evaluation, and reporting systems; capacity building, deployment of new generation control tools; as well as education and communication strategies in order to act on the basic causes of NTDs (18). These actions require a thorough change in the health system of LICs, not an easy goal to reach due to the weakness of the system and the lack of health education. In the case of trachoma, it will take a lot of effort to eliminate it, maybe more than the other NTDs analyzed, because a successful elimination of trachoma depends not only on treatment but also on external factors that cause the disease. Lack of sanitation and clean water are the most important factors. A

study carried out on children in 16 communities in Ethiopia shows that the infection rate had been reduced from 63.5% to 2.6% after MDA, but returned to 25.5% 18 months after the treatment ended. In Maly, three years after the MDA program had been completed, the prevalence of trachoma increased in one area from 3.9% to 7.3% and in another from 2.7% to 8.2% *(114,115)*.

The DDPs investigated represent a milestone in the partnerships formed to tackle NTDs, for the efforts made, the cost effective strategies implemented, the millions of people treated and the results reached. The success of NTDs control programmes is the result of national government and donor commitment; clear objectives; realistic time frames (long enough to obtain positive outcome); use of targeted effective interventions; the PPPs for the coordination of the programme; long-term stable financing; drug donation; monitoring and evaluation systems *(106)*.

In the PPPs the intervention of the private sector is one of the most important elements that turns the DDPs into cost effective interventions. In fact the economic success is primarily due to the donation of treatment free of charge, as explained before. An important contribution also derives from governments, NGOs, and communities that contribute to manage the programme activities, and often also intervene financially.

Huge efforts have been made for NTDs, and after the London Declaration the attention of international stakeholders was raised more than ever, but they still have to continue, starting with the issues that rose from the past. As remarked by WHO, the integration of interventions is of primary importance, in order to reduce the costs of implementation and the resources used. It is of primary importance that NTDs become a part of the larger development agenda at global level, where PPPs established so far represent just an example to follow *(15)*.

The step forward in my research is represented by critical qualitative-quantitative analysis of the issues derived form the DDPs analyzed, with particular interest in the economic analysis, in order to assess the factors that contribute to the variation among data available.

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