Operational lessons from 20 years of the Mectizan Donation Program for the control of onchocerciasis

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Summary

The donation of ivermectin (Mectizan®, Merck & Co., Inc.) to control onchocerciasis (river blindness) was established in 1987 and has since gradually expanded to provide for >570 million treatments cumulatively over the past 20 years. The Mectizan Donation Program (MDP) operates within a broad partnership in 33 endemic countries in need of mass treatment. Particular operational methods and tools are applied to facilitate ivermectin mass treatment. Drug management has been streamlined, including dosing, tablet size and packaging, and monitoring for adverse events. Much of the experience gained in the development of ivermectin mass treatment can be usefully applied in the recent broader perspective of control of neglected tropical diseases. The most important operational lessons of the MDP include: (i) the need to easily define the target population for treatment using rapid, non-invasive techniques; (ii) the value of a broad partnership; (iii) the great potential of working through community-directed treatment; (iv) the need to streamline all drug management aspects and (v) the importance of operations research to tackle new challenges.

keywords onchocerciasis, ivermectin, mass treatment, operations research, partnership

Introduction

Onchocerciasis has been the subject of control since the 1940s, when vector control was first applied (Thylefors 2004). It was not until the early 1980s, when clinical trials demonstrated the microfilaricidal effectiveness of ivermectin against Onchocerca volvulus, the cause of human onchocerciasis (Aziz et al.1982), that a mass treatment strategy could be envisioned. In 1987, ivermectin was registered for human use (Mectizan®, Merck & Co., Inc.). Later the same year, Merck announced the donation of Mectizan® with the goal of making available, free of charge, as much ivermectin as needed, for as long as needed, for the elimination of onchocerciasis as a public health problem in all endemic countries (Collins 2004).

The application of mass treatment with Mectizan over two decades has shown great progress; however, a number of technical, operational and programmatic challenges have been encountered and successfully addressed. A wealth of experience has been gained with many lessons for other current and future public–private partnerships for drug donations (Sturchio & Colatrella 2002); the present review deals with those lessons of a technical and operational nature, which have not previously been addressed or fully discussed.

Defining the target population

The first and urgent challenge when ivermectin became available was to be able to easily decide which communities needed treatment and setting operational priorities. Those most severely affected by the disease should preferably have rapid access to treatment.

Two rapid assessment methodologies at the community level were therefore developed. First, instead of performing invasive skin snips, the palpation of onchocercal nodules provided an easy and non-invasive solution, as it was discovered that the prevalence of palpable nodules in males is roughly half of the prevalence determined by skin snip (Taylor et al. 1992). This method of Rapid Epidemiologic Assessment (REA) has been successfully applied in thousands of communities allowing for prioritizing and limiting of mass treatment to hyper- and meso-endemic communities (Burnham & Mebrahtu 2004) vs. clinic-based individual treatment which is recommended in hypo-endemic areas (<20% nodule prevalence). Meso- and hyper-endemic communities are those defined by a nodule prevalence of 20% or greater.

A further step of mapping is needed, however, to avoid having to examine a very large number of communities. Onchocerciasis, being a vector-borne disease related to

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watercourses with breeding sites for *Simulium* flies, allows for quite reliable conclusions as to likely disease transmission and extension based on geographical criteria. A broad assessment of endemic areas can thus be made on the basis of ecology (savannah, rainforest, known breeding sites, *Simulium* species, etc.) as a Rapid Epidemiologic Mapping of Onchocerciasis (REMO), which is based on the above and a survey of communities (applying REA) likely to be at the highest risk (Ngoumou & Walsh 1993).

The combined use of REA and REMO has been extremely useful and important in delineating program operations in Africa (Ngoumou et al. 1994). Almost all areas likely to be eligible for onchocerciasis mass treatment in the countries included in the African Programme for Onchocerciasis Control (APOC) have now been assessed by that Programme (APOC/WHO 2006) working in collaboration with National Onchocerciasis Task Forces (NOTFs) (Figure 1).

**The challenge of reaching out and involving the community**

Initially ivermectin was distributed on a small scale through a mobile-team approach (WHO 1995). Great attention was paid to weighing all patients for dosage, and to active surveillance for adverse reactions. As more experience was gained and ivermectin proved to be a very safe drug in most circumstances, more flexibility was allowed in dosing and a passive surveillance system for adverse reactions was adopted (Brown 1998). Still, an obstacle to rapid up-scaling of treatment was the lack of health staff and resources for the mobile teams. This challenge was addressed by a group of non-governmental development organizations (NGDOs), and an NGDO Coordination Group for ivermectin distribution was established with WHO in 1991 (Drameh et al. 2002). This led to a first set of guidelines for the use of ivermectin, based on the NGDO field involvement (WHO 1991). The NGDOs came to play a critical role in support of ivermectin distribution through their work with Ministries of Health, their expertise in program management, and their financial support. They have also contributed to the development of appropriate communication strategies for the population targeted for mass treatment with the goal of achieving high coverage and compliance (Haselow et al. 2003).

After several rounds of ivermectin mass treatment, the endemic communities would often become quite knowledgeable and interested, and the beneficial effects of ivermectin would usually be much appreciated (Tielsch &

![Figure 1](image-url) Overview of the Rapid Epidemiological Mapping of Onchocerciasis in the African Programme for Onchocerciasis Control (APOC) area, 2006. Reproduced with permission and courtesy of APOC.
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Beeche 2004). This led the United Nations Development Program/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR) to start a series of investigations of possible community involvement in the treatment itself (WHO/TDR 1996). The Community-Directed Treatment with Ivermectin (CDTI) strategy implied that a well-informed and motivated community could select its own drug distributors, if the handling of the drug was straightforward enough in terms of safety and dosing and appropriate records could be kept. The TDR studies demonstrated the interest and capability of communities to undertake their own treatment of ivermectin, and this led to rapid progress of cost-effective CDTI schemes (WHO/TDR 2000; Amazigo et al. 2002). A number of operational issues ensued, however, from the selection of the Community Directed Distributors (CDDs), to reporting requirements, incentives, and links to other similar health interventions. As more experience has been gained, it seems clear that CDTI is a great success overall with extremely good coverage in many settings, but there are also some shortcomings such as a considerable attrition of CDDs in the absence of financial incentives; this is still a critical question for the future sustainability of the CDTI (Burnham & Mebrahtu 2004). Another weakness is the poor maintenance of records (Amazigo et al. 2002).

Building partnerships

The unique and broad-based partnership that has evolved around onchocerciasis control is extremely important and helpful to the ivermectin mass treatment efforts, bringing about results that no single party could achieve (Peters & Phillips 2004). The executive role of WHO in the Onchocerciasis Control Programme in West Africa (OCP) and subsequently in APOC and the Onchocerciasis Elimination Programme for the Americas (OEPAC) along with the World Bank as fiscal agency, implied access to technical capability and needed resources. This was further reinforced by the NGDOs input both in managerial and financial terms, including the new formula of NOTFs which include staff from the Ministries of Health in all endemic countries.

This partnership also gives opportunities for more broad-based interventions than just the drug donation (e.g. vitamin A supplementation), which is important in building a public-health program. Even if the drug may account for a significant cost of treatment, it is just one component in the overall chain of distribution logistics and reporting (Colatrella 2003). Support to strengthen national capacity is badly needed in all endemic countries, to allow for integration of the drug donation into the peripheral healthcare system; there is, however, increasing competition between programs for limited resources (Burnham & Mebrahtu 2004).

The Mectizan Expert Committee and the Mectizan Donation Program

The Mectizan Expert Committee (MEC) was established in conjunction with the Mectizan Donation Program (MDP), to function as an independent decision-making body with expertise for addressing all aspects of the public health application of ivermectin treatment. The MEC originally spent considerable time reviewing applications for ivermectin, but it has gradually taken on a number of other challenges. Thus, the drug management issues discussed below were all handled through the MEC in its advisory capacity to Merck & Co., Inc. Further, when the first case of neurologic Loa-loa-related Serious Adverse Experiences (SAEs) including encephalopathy became known, the MEC immediately recommended a scientific consultation to collect and discuss all available evidence (Anonymous 1991; Ducorps et al. 1995) Scientific working groups on L. loa and the relationship with ivermectin treatment were therefore convened in 1995 (for development of case definitions), 1998 (describing the clinical course) and 2002 (to discuss the risk-benefit of ivermectin treatment in loiasis-endemic areas, and to develop a research agenda) (MDP 2003).

The MEC has also developed specific guidelines for the treatment of onchocerciasis in L. loa-endemic areas, and these have been broadly disseminated in all countries concerned (Alleman et al. 2006). The issue of reporting of SAEs from the field has also been reviewed by MEC, as has the eligibility criteria for treatment and their field application in certain cases, such as with manifest epilepsy (Twum-Danso 2003, 2004).

The MDP was established to handle the day-to-day operations of Merck’s donation and to serve as secretariat for the MEC. Thus, the MDP develops meeting agendas, prepares technical backgrounds, and implements recommendations made by the MEC with the input of other partners as needed. A major responsibility of the MDP is to perform technical reviews of requests for ivermectin from mass treatment and clinic-based programs. The MDP also prepares regularly forecasts for ivermectin needs for Merck’s production planning. The MDP has a system for monitoring treatments, so that progress towards the world-wide ultimate treatment goal (>100 million treatments annually) and 100% geographic coverage can be tracked. Oversight of the surveillance, clinical management, reporting and analysis of SAEs following treatment also fall under the purview of the
MDP, which has developed a research agenda (MDP 2003) designed to address issues related to the drug’s safe use.

Since Mectizan was first donated in 1988 and through 30 June 2007, enough drug has been approved cumulatively for more than 570 million treatments for onchocerciasis (Figure 2).

**Drug management**

**Safety**

The clinical trials of ivermectin undertaken in the 1980s led to a recommended dosage of 150 mg/kg bodyweight as a single dose. Much higher doses have been studied without any additional efficacy against *O. volvulus* and few toxic effects (Awadzi et al. 1985; White et al. 1987; Gardon et al. 2002). Adverse reactions are usually mild and of short duration, and annual treatments are well-tolerated (Tielosch & Beeche 2004). Thus, ivermectin was proven to be a very safe drug that could be given to all eligible people in a community except pregnant women, children <15 kg of bodyweight (or later <90 cm of height), individuals with a hypersensitivity to ivermectin or with serious illnesses of an acute or chronic nature.

Loiasis constitutes an obstacle to ivermectin mass-distribution in several African countries, in particular in parts of Angola, Cameroon, and the Democratic Republic of Congo because of the potential for neurologic SAEs, including coma, following treatment of onchocerciasis in areas of co-endemicity (Boussinesq 2006). These cases occur very rarely, and only in individuals with very high *Loa* microfilarial counts, but require rapid referral and symptomatic management in a hospital.

**Dosing**

In the use of ivermectin at the community level, it was soon realized that there were a few constraints to effective mass treatment. In particular, the need to weigh each patient and then calculate how many tablets would be needed was labour- and time-intensive. It also implied the cost and trouble of obtaining and maintaining weighing scales. As it was realized that the dosage of ivermectin could be fairly flexible, alternative options were investigated for determining the dose. A large trial in Nigeria demonstrated that height, instead of weight, could be used to determine dosage, and a simple measuring stick labelled with the number of tablets in relation to height was found to be an effective tool (Alexander et al. 1993). The new system of having a dosing pole was quickly accepted in national programs and greatly facilitated the handling of larger numbers of treatments (Figure 3).

**Tablet size**

The originally produced Mectizan tablets were 6 mg and were packaged in individual foil envelopes. This tablet formulation and packaging were found to be impractical in community-based treatment settings where a large number of tablets had to be extracted from foil envelopes and then
divided into halves for correct dosing. This matter was brought to the attention of the MEC in the 1990s by APOC and NGDOs, leading to a recommendation that 3-mg tablets should be manufactured. Merck accepted this proposal and undertook the process of testing, registering and manufacturing the new 3-mg tablet formulation. The 3-mg tablets became available in September 1997 packaged in plastic bottles of 500 tablets (Mectizan Program Notes, issue 19, 1997) [These references are available from MDP on request]. The changes in formulation and packaging were welcome simplifications and save time in the handling of the drug in mass treatment.

Shelf-life

The shelf-life of a drug is very important as there may be considerable delays in shipping arrangements, customs clearance and in-country handling. The drug may also be subject to unsuitable storage, in terms of temperature, humidity, etc. Mectizan tablets originally had a shelf-life of 1 year, but to improve upon this, Merck undertook a study of drug storage under varying conditions and time intervals making it possible to extend the official shelf-life of the 3 mg Mectizan tablets from one to two, and ultimately 3 years as from 2002; this has the potential to reduce wastage, as it allows for tablets remaining from one treatment cycle to be used in the next cycle (Mectizan Program Notes, Issue 30, 2002) [These references are available from MDP on request].

Pregnancy

The use of ivermectin during pregnancy is contraindicated. Pregnancy is a common concern in mass treatment scenarios because mass treatment does not lend itself to individual screening. Simple self-reporting by women has, however, proven to be valuable (Chippaux et al. 1995).

A major community-based study was undertaken in Liberia in which women that had been inadvertently treated during pregnancy and non-treated women were monitored longitudinally. The outcome indicated no differences in birth defects between children born to treated, vs. non-treated women (Pacque et al. 1990). A similar, more recent, study in Ghana, where ivermectin and albendazole were given simultaneously in the context of mass treatment for the lymphatic filariasis elimination program, gave the same results (Gyapong et al. 2003). Reassuring as these data may be, Mectizan treatment during pregnancy is still contraindicated unless the medical supervisor of the field program or the treating physician in a clinic/hospital deems that the benefits of treatment outweigh any potential risks.

Monitoring and management of adverse experiences

Since the beginning of the program, substantial attention has been placed on monitoring and managing adverse experiences following ivermectin treatment, particularly the serious cases that require medical intervention. Most adverse experiences are mild, transient and responsive to symptomatic treatment such as analgesics and antihistamines (Awadzi et al. 1985; De Sole et al. 1989). However, any case that results in death, a life-threatening adverse drug experience, in-patient hospitalization or prolongation of an existing hospitalization, persistent or significant disability/incapacity, congenital anomaly or birth defect, cancer or overdose (accidental or intentional) is considered a SAE by international standards [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)]. All
SAEs following ivermectin treatment must be reported to Merck, which is then required to report them to the drug safety and regulatory agencies in the USA and internationally.

MDP/MEC, Ministries of Health and APOC have played a key role in ensuring best practices are applied for surveillance of SAEs at the community level, referral and evacuation to health facilities, clinical management and reporting. The SAE reporting form, itself, has been revised several times during the 20-year history of the program based on feedback from clinicians and public health administrators in the field. MDP and the MEC have provided additional technical support to countries in which onchocerciasis and loiasis are co-endemic where there is a risk of neurologic SAEs in individuals with high intensity L. loa infections (MEC/TCC Recommendations 2004) [These references are available from MDP on request].

Operations research

Today, the issues of ivermectin mass treatment management have been largely addressed, whereas new challenges, such as integration of CDTI into a country’s health system, and co-implementation of other health interventions are being faced. These new opportunities will require a broad range of research studies, including technical and managerial aspects, as well as community acceptance and long-term sustainability.

The unforeseen challenge of co-endemicity of onchocerciasis and loiasis in parts of central Africa illustrates the need for research as part of a field program for drug donations. The development of a new rapid assessment technique for L. loa by WHO/TDR (i.e. RAPLOA) is particularly useful in allowing for an easier mapping of that disease and its intensity (WHO/TDR 2001). Research efforts on loiasis are supported by MDP collaborating with national teams in endemic countries.

Another important research issue is to define an endpoint strategy for ivermectin treatment in Africa (Hopkins et al. 2005). Available modelling data point to annual treatments for more than 25 years as being needed to eliminate infection (Winnen et al. 2002). A major TDR study is ongoing to elucidate the results obtained after more than 18 years of regular annual, or in some instances twice-yearly, ivermectin treatment in selected West African foci. It is hoped that in some isolated areas of less intense infection and transmission, it will be possible to stop treatment after such long-term use. The option of more frequent administration of ivermectin is also of great interest to possibly allow for elimination of the disease; this will require careful consideration of the epidemiological and therapeutic circumstances in all endemic foci (Cupp & Cupp 2005; Thylefors & Alleman 2006).

The most important lessons

The following are the most important operational lessons learned by the MDP in its 20 years of operations:

- appropriate assessment tools to easily identify target populations for treatment;
- a broad partnership with a clearly recognized common agenda and identified roles for all parties;
- an appropriate community base for treatment with motivation and local support;
- streamlining of all drug management aspects; and
- an ongoing operations research agenda to address present and upcoming challenges.

Future perspectives

While there is a clear opportunity to eliminate onchocerciasis from the western hemisphere over the next few years through continuing ivermectin treatment, the prospects for elimination in African endemic countries will be more complex. In much of Africa there will be a need for sustainable long-term ivermectin distribution, and as the onchocercal disease manifestations dwindle and compliance with treatment potentially decreases, there will be a need to link ivermectin distribution to other compatible interventions, such as ‘neglected tropical diseases’ control. A number of new opportunities are available today for large-scale preventive chemotherapy against those diseases, as long-term drug donations are available, in particular against lymphatic filariasis, intestinal helminths, schistosomiasis and trachoma (WHO 2006). If a macrofilaricidal drug were to become available, it could obviously allow for a much more rapid elimination of onchocerciasis in Africa.

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