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Impact of ivermectin on illness and disability associated with onchocerciasis

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Summary The Onchocerciasis Control Program (OCP), one of the most successful vertical disease control programs in the history of public health, came to an end in 2003 with devolvement of responsibilities for control program activities passed to the countries affected. Fortunately, 15 years ago the Mectizan® Distribution Program (MDP) was founded to provide a complementary approach to controlling the disabling consequences of this parasitic infection. With over 250 million doses of ivermectin distributed over the past 15 years, the MDP is well on its way to both solidifying the progress made by the OCP and extending program reach well beyond the boundaries of the OCP. Through the extensive clinical testing protocols implemented in a variety of countries in Aftica, ivermectin has been proven to be a safe and highly effective treatment for onchocerciasis. Regular distribution to populations living in endemic areas has demonstrated significant reductions in blinding ocular complications, transmission, and disability caused by onchocercal skin disease. As yet undocumented, are the likely significant impact regular population dosing with ivermectin has on intestinal helminth infections, lymphatic filariasis, and human scabies infection. While there are significant barriers to continued program success, focussed attention on expanding and improving community-directed ivermectin distribution is likely to lead to further progress against this resilient infection.

keywords ivermectin, disability, onchocerciasis, Mectizan

Introduction

The 15th anniversary of the Mectizan® Distribution Program (MDP) in 2002 marked an important milestone in the continuing efforts to control the adverse consequences of onchocerciasis. The early post-licensure field trials provided strong evidence that the widespread distribution of ivermectin could complement the vector control strategies underway in West Africa and offer the potential to reduce the burden of onchocercal blindness and skin disease in areas outside those covered by the Onchocerciasis Control Program (OCP). The past 15 years have provided early evidence that the widespread use of ivermectin (over 250 million doses over the past 15 years) in communities endemic for onchocerciasis may live up to these high expectations. However, since 2003 the challenge has been even greater as one of the most successful vertical disease control programmes in history comes to an end. The WHO-managed, multi-country OCP will end and full responsibility for onchocerciasis control will devolve to the countries. This will place a significant additional burden for continued control on the MDP while we wait for the development of a safe, effective, and simple to deliver macrofilaricide.

This paper reviews the clinical development and testing of ivermectin for onchocerciasis, the available data on its impact on blindness and disability, and its ancillary benefits for other parasitic disorders highly prevalent in those countries affected by onchocerciasis.

Human trials of ivermectin for treatment of onchocerciasis impact on microfiladermia

Twenty years ago, ivermectin was known as a safe and effective anthelminthic drug for use in combating a variety of parasitic nematodes in animals. Its widespread use and therapeutic profile suggested that it might also be useful for the treatment of *Onchocerca volvulus* in humans. However, the tolerance of the drug in humans was unknown and there was concern that a highly effective microfilaricide like ivermectin might produce the same severe inflammatory reactions seen with diethylcarbamazine (DEC). Despite concern that adverse results in human trials might undermine ivermectin's use in veterinary medicine, Merck supported initial clinical testing of ivermectin for use in treating onchocerciasis. Phase one trials were promising. Relative to DEC and placebo, ivermectin resulted in significant and longer lasting decreases in

microfilarial skin loads, and most adverse effects were mild and non-ocular (Brown & Neu 1990).

Phase two studies were conducted in Liberia, Senegal, Ghana and Mali. Doses ranged from 50 to 100 μg/kg and again, substantial decreases in microfilarial skin loads were observed. Furthermore, corneal and anterior chamber loads of microfilaria were greatly reduced and there was little indication that Mazzoti-type reactions occurred. The reduction in skin and eye microfilaria loads were prolonged and maintained for approximately 9 months (Greene *et al.* 1985; Lariviere *et al.* 1985; Awadzi *et al.* 1986; Diallo *et al.* 1986).

Phase three studies were conducted in Cote D'Ivoire, Ghana, Guatemala, Liberia, Mali, and Togo. Patients received either 100, 150, or 200 μg/kg of ivermectin, although no differences between regimens were apparent after 3 months. Skin and eye microfilaria loads remained low after 1 year, and adverse reactions were mild, with no adverse reactions occurring in the eye (White *et al.* 1987). As a result of the minimal ocular and systemic side effects of treatment, it was decided that ivermectin would be safe for mass distribution (Taylor & Greene 1989a). This series of studies suggested that a dose of 150 μg/kg was adequate to produce a sustained reduction in microfilarial skin loads with an acceptable safety profile. As a result, ivermectin was registered in France in 1987.

Given that adult *O. volvulus* can live 12–15 years, and that ivermectin is primarily a microfilaricide, it was anticipated that once distribution programmes began, regular treatment would be required for at least 15 years before it would be safe to stop in any particular community. It was also assumed that, as the ocular complications associated with significant visual loss in onchocerciasis were not reversible, an extended period of ivermectin distribution would be required before significant reductions in the cross-sectional prevalence of blindness and visual impairment would be observed.

Post-licensure studies followed the phase three trials and were conducted primarily in West Africa. These large community studies were designed to evaluate the effectiveness, safety, and acceptability of ivermectin at the community level and to provide preliminary evidence related to the impact of regular ivermectin dosing on transmission. From 1987 to 1988, eight community-based studies were conducted within the OCP area and five were conducted in areas outside the OCP. The study communities represented various epidemiological conditions including hyper- and meso-endemic areas with and without vector control (Dadzie *et al.* 1987, 1989a, 1991; Taylor *et al.* 1989b). These studies suggested that annual ivermectin treatment might be sufficient to control ocular disease caused by onchocerciasis, even in areas of high endemicity.

The effects of ivermectin on microfilaridermia were evaluated with longitudinal skin snip surveys. The overall effect of ivermectin treatment in the various study areas was a reduction of 96–99% in skin microfilariae within the first few months of treatment (Remme *et al.* 1990). However, the time to recrudescence varied between areas. Ivermectin treatment was also associated with decreases in the number of microfilariae found in onchocercal nodules in the post-licensure studies (Albiez *et al.* 1988).

The multi-year follow-up studies have shown a significant impact on decreasing microfilarial skin loads. After 5 years of treatment in Asubende, there was a 90% reduction in skin microfilaria (Alley *et al.* 1994). In Gami, Central African Republic, a drastic reduction in both the prevalence and intensity of *O. volvulus* microfilaridermia was observed after 5 years of annual treatment in the community (Kennedy *et al.* 2002). Repeated doses of ivermectin appear to have a cumulative effect, and multiple annual doses of ivermectin have resulted in a slower repopulation of the skin by microfilariae (Whitworth *et al.* 1992).

Impact on adult *Onchocerca volvulus*

A variety of studies have been conducted to estimate the potential effects ivermectin might have on adult *O. volvulus*. The majority of these studies used the standard dose of ivermectin (150 μg/kg), and varying re-treatment regimens. Higher doses of ivermectin did not enhance any effects of the drug on adult *O. volvulus*. No additional impact on adult *O. volvulus* was observed when 800 μg/kg every 3 months was used compared with standard doses (Gardon *et al.* 2002).

The effect of ivermectin on the reproductive cycle of adult *O. volvulus* has been well described in the literature. Although there is controversy on some aspects of this relationship, it is reasonably clear that multiple doses of ivermectin have little direct impact on oogenesis (Duke *et al.* 1990; Chavasse *et al.* 1992; Kläger *et al.* 1996). There is some effect on fertilization of adult females with increasing doses associated with significant reductions in the proportion of female worms containing sperm (Duke *et al.* 1991, 1992; Chavasse *et al.* 1993), although the spermatozoa themselves are normal (Albiez *et al.* 1988).

Multicellular stages develop within the female *O. volvulus* uterus and are released from the vulva as stretched microfilaria. This development is impeded by multiple doses of ivermectin, likely because of paralysis of the lower uterus (Duke *et al.* 1992). This results in an accumulation of normal and degenerating microfilaria, which intensifies after multiple treatments (Awadzi *et al.* 1986; Albiez *et al.* 1988; Chavasse *et al.* 1992). It is likely that ivermectin's impact on fertilization is indirect and a

result of obstruction of the uterus with degenerating microfilariae (Albiez *et al.* 1988; Chavasse *et al.* 1992).

Both single and multiple doses of ivermectin are associated with fewer adult males in nodules (Awadzi *et al.* 1985; Greene *et al.* 1985; Duke *et al.* 1990, 1992; Gardon *et al.* 2002). In contrast to adult females, adult males are mobile and capable of inseminating females residing in different nodules. It has been postulated that ivermectin may alter the mechanisms that allow adult *O. volvulus* to locate each other. This could account for males' migration from nodules after multiple treatments. The males' migration may also account for the decrease in inseminated females observed after numerous ivermectin dosages (Duke *et al.* 1992).

Results from a variety of studies suggest that repeated ivermectin doses results in an increase in the proportion of dead and moribund adult worms, primarily females (Duke *et al.* 1990, 1991, 1992; Chavasse *et al.* 1992; Gardon *et al.* 2002). Nonetheless, the majority of adult worms appear to remain unaffected, healthy, and capable of reproducing (Duke *et al.* 1990; Kläger *et al.* 1996). While ivermectin does have a significant effect on adult *O. volvulus*, its role in onchocerciasis control is clearly dominated by its microfilaricidal activity.

Wolbachiae

Wolbachia endobacteria are symbionts of arthropods and are also found in filarial nematodes, including *Onchocerca volvulus*. Recent evidence suggests *Wolbachia* bacteria contribute to the inflammatory pathology associated with disease (Taylor & Hoerauf 1999; Saint André *et al.* 2002). There is a symbiotic relationship between *Wolbachia* endobacteria and *O. volvulus*, and its depletion has a long-term adverse impact on worm fertility. In Ghana, 6 weeks of daily doxycycline resulted in almost complete depletion of *Wolbachiae* by 11 months and an inhibition of embryogenesis in female *O. volvulus* (Hoerauf *et al.* 2000, 2001). Among patients receiving both ivermectin and doxycycline, there was an absence of microfilaridermia in more than 90% and very low microfilariae intensities in the remaining cases. In participants receiving ivermectin alone, microfilariae began to recrudesce within 4 months of treatment (Hoerauf *et al.* 2001). These data suggest that treatment for *Wolbachiae* infection may be complementary to ivermectin in controlling onchocerciasis and its associated morbidity (Saint André *et al.* 2002). However, the extended doxycycline regimen required for a significant impact on fertility is currently impractical for a mass chemotherapy approach. Nonetheless, the concept of an effective, safe and easily administered drug that can cause permanent sterility in adult *O. volvulus* through its impact on *Wolbachiae*, may be just as important as a macrofilaricide for future progress in onchocerciasis control.

Safety of ivermectin

Ivermectin is a safe and well-tolerated drug. The incidence, but not severity, of adverse effects attributed to ivermectin is related to the pre-treatment intensity of microfilariae in the skin (De Sole *et al.* 1989; Rothova *et al.* 1989; Chijioke & Okonkwo 1992; Zea-Flores *et al.* 1992; Njoo *et al.* 1993). In endemic areas, the intensity of microfiladermia increases with age corresponding to the higher incidence of adverse reactions observed in persons 20 years of age or older in communities using mass distribution of ivermectin (Zea-Flores *et al.* 1992). No deaths attributed to ivermectin treatment have occurred in mass chemotherapy safety trials (De Sole *et al.* 1989; Pacqué *et al.* 1991a; Zea-Flores *et al.* 1992). Furthermore, the incidence of adverse reactions caused by ivermectin in these community studies has been lower than the incidence reported in the clinical trials (De Sole *et al.* 1989).

The most common adverse effects attributed to ivermectin treatment were oedema, fever, puritis, and pain, although their relative frequency varied among sites (Pacqué *et al.* 1991a; Chijioke & Okonkwo 1992; Zea-Flores *et al.* 1992). Most adverse reactions occurred within 24–48 h after treatment, and were mild to moderate in severity, transient, and manageable by primary health-care workers. These reactions are generally self-limiting and become less severe with subsequent treatments (Pacqué *et al.* 1991a; Chijioke & Okonkwo 1992; Zea-Flores *et al.* 1992). Few adverse reactions are severe and have included severe sustained postural hypotension and dyspnoea, the latter was not observed in the clinical trials (De Sole *et al.* 1989; Chijioke & Okonkwo 1992).

The original guidelines for use of ivermectin in community-based distribution programmes call for excluding pregnant women, children younger than 3 years, and women nursing infants under 3 months. There have been no trials that have specifically assessed ivermectin's impact on pregnant women and their newborns; however, this issue has been addressed as a part of the large, post-licensure studies. In a 3-year community-based study in Liberia, only 31% of pregnant women were aware of their pregnancy during the ivermectin dosing rounds, and 50% of these would be treated unintentionally during the first trimester if routine pregnancy testing was not a part of the distribution protocol. Among the dosed and non-dosed pregnant women, no significant difference in birth defects was detected (Pacqué *et al.* 1990a). These results have led to increased flexibility in the population eligible for ivermectin treatment. Where the risk of blindness is high,

treatment has been extended to include pregnant women or women that have been nursing for at least 1 week (Brown 1998). Neither the incidence nor the severity of side effects of ivermectin treatment is associated with concurrent intestinal parasitic infection. On the contrary, ivermectin treatment gives the additional benefit of significantly reducing *Ascaris lumbricoides* worm loads (Njoo *et al.* 1993). Additional trials have shown that dosages 10 times above the highest FDA approved dose (200 μg/kg), as well as regimens consisting of higher than standard and more frequent doses, were shown to be well tolerated with no central nervous system toxicity (Guzzo *et al.* 2002).

Ivermectin's safety, ease of administration, and high efficacy for both onchocerciasis and ascariasis has led to its wide acceptance among communities endemic for onchocerciasis (Pacque *et al.* 1989; Pacqué *et al.* 1990b).

Impact on transmission

When microfilarial skin loads decline, blackflies take up fewer microfilariae with each blood meal (Cupp *et al.* 1986; Prod'hon *et al.* 1987). The uptake of fewer microfilariae results in the production of fewer infective L3-stage larvae, which in turn, affects the annual transmission potential (ATP) resulting in a lower intensity of transmission (Cupp *et al.* 1986). In Liberia, after two annual doses of ivermectin, the number of infective flies with L3 larvae was reduced by 82–89%, and a 63–97% reduction in the intensity of transmission was observed (Trpis *et al.* 1990). In Ghana, a reduction in transmission intensity of 65–85% was observed 3 months post-treatment (Remme *et al.* 1989).

In addition to this standard approach for assessing transmission, young children have been used as sentinel populations for assessing initial infections with *O. volvulus*. As the majority of children under 5 years of age have not been treated, this approach allows the identification of incident *O. volvulus* infections. Results have demonstrated a significant impact of mass ivermectin chemotherapy on decreasing transmission. In Senegal and Guinea Bissau, no new infections in children aged 0–5 years were detected after eligible persons within the community had been treated with ivermectin (Boatin *et al.* 1998). In Liberia, after only 2 years of ivermectin distribution among persons older than 12 years of age, the prevalence of infection in 5-year-old children decreased by 21%, and a reduction of 45% in the incidence of infection in 7–12-year-old children was observed (Taylor *et al.* 1990). Finally, in Cameroon, the prevalence of skin microfilariae and mean microfilarial skin densities were reduced by 55% and 77% respectively in 5–7-year-old children that had never been treated with ivermectin (Boussinesq *et al.* 1995).

In areas with seasonal *O. volvulus* transmission, it has been suggested that the most effective use of ivermectin would be to treat high-risk populations just prior to the period of highest vector density. In Mali it was shown that treated individuals remained non-infective to competent blackflies for up to 6 months post-treatment. This time interval was considerably longer than the 3-month vector-breeding period during which intense transmission occurs (Cupp *et al.* 1986). In addition, ivermectin is an effective prophylactic agent against juvenile worms in the bovine model (Tchakoute *et al.* 1999). If a similar effect occurs in human infection, this supports the argument for timing ivermectin distribution just prior to the high transmission season.

In the Americas, mathematical modeling suggests that twice-yearly treatment and high coverage (85% or higher) can eliminate the infection in the Guatemalan foci. In Africa, elimination of infection is a longer-term goal and there remain serious questions about its feasibility. Mathematical models suggest that periods of over 35 years will be required for areas with medium or greater levels of endemicity, significant heterogeneity in prevalence, and annual treatment with modest coverage of 65% (Winnen *et al.* 2002). There is some concern that the models used to make these projections do not adequately account for a variety of factors that can affect their estimates (Borsboom *et al.* 2003). A recent review of programme performance data from the OCP areas suggests that elimination of transmission is unlikely in most situations and that programs may be required for the foreseeable future (Borsboom *et al.* 2003).

Impact of chemotherapy with ivermectin on blindness caused by onchocerciasis

Impact of combined ivermectin and vector control

The OCP proved that vector control was an effective approach to controlling onchocerciasis. Over the period of OCP operations, it was responsible for 25 million hectares of land for resettlement and agriculture, more than 35 million people freed of *O. volvulus* infection, and the prevention of >2 00 000 cases of blindness (Molyneux 1995). While vector control can be highly effective when performed well, control of ocular onchocerciasis occurs more rapidly when both ivermectin chemotherapy and vector control are practiced concurrently (Abiose 1998). Mathematical modelling suggests that the duration of vector control required to reduce recrudescence to less than 1% could be reduced from 14 to 12 years when combined with annual ivermectin treatment at a coverage of only 65–70% (Molyneux 1995; Plaisier *et al.* 1997). However,

this combined approach is unlikely to be implemented in the future except in selected locations.

Impact of ivermectin chemotherapy without vector control

The African Program for Onchocerciasis Control (APOC) was established to maintain and extend the success of the OCP in areas endemic for onchocerciasis outside the OCP. A similar programme has been established in the Americas, the Onchocerciasis Elimination Program of the Americas (OEPA), but the disease is highly focal and of only modest intensity in these populations. Both programmes use a strategy based on the distribution of ivermectin at the community level. Significant impact on ocular onchocerciasis has been observed in APOC areas. In a holoendemic area of Ghana, ocular microfilarial loads in the anterior chamber and cornea decreased to 20% and 10% of pretreatment levels (Dadzie *et al.* 1990). Reduction in the prevalence of ocular lesions including sclerosing keratitis, iridocyclitis, and optic atrophy have been observed however, the reductions have not been significant in all studies, likely because of the relatively limited follow-up period (Dadzie *et al.* 1991; Whitworth *et al.* 1991; Cousens *et al.* 1997; Abiose 1998; Kennedy *et al.* 2002). The lack of significant impact of chemotherapy on already present severe ocular disease suggests that the prevalence of these advanced signs will decline slowly over time as these individuals die and the population becomes characterized by persons with low or absent microfilarial loads. Estimated numbers of cases of blindness avoided based on the initial 15 years of ivermectin distribution are difficult to obtain as the distribution of various *O. volvulus* strains, their intensity of infection, and their pathogenicity is not as well understood as it was for the OCP area. However, given the significant reductions in microfilarial infection achieved with regular ivermectin distribution, these numbers are likely to already approach that observed over a similar period of time with intensive vector control.

The most important question for APOC and for the OCP areas is whether mass treatment with ivermectin alone can achieve and/or maintain the burden of infection adequate to achieve control programme objectives. As elimination of infection is unlikely, most observers have settled for programme objectives that call for control of ocular and other systemic morbidity caused by onchocerciasis. Data from the OCP areas suggest that dramatic reductions in risk of blindness have been achieved with ivermectin alone (Borsboom *et al.* 2003). However, continued transmission requires that control programme efforts be extended indefinitely.

Impact of ivermectin on other morbidities

Onchocercal skin disease

Until recently, the importance of onchocercal skin disease (OSD) as a disabling condition was underestimated. In addition, the geographic distribution of OSD did not match that seen for the ocular complications of onchocerciasis. The reason for this discrepancy is unclear but is likely because of differences in strains of *O. volvulus*. OSD tends to occur with higher prevalence in forest areas, while ocular disease and blindness are more prominent in Savannah regions (Dadzie *et al.* 1989b). Even after the introduction of ivermectin distribution as a control strategy, communities plagued primarily by OSD were not targetted for mass chemotherapy.

Skin reactions to *O. volvulus* infection vary, and the montage includes depigmentation, skin lesions, itching, and dermal atrophy. Troublesome itching was found to be one of the most important symptoms of onchocerciasis in a Pan-African study conducted to evaluate the importance of OSD (World Health Organization 1995). Strong associations have been found between the prevalence of skin lesions and troublesome itching and onchocercal endemicity (World Health Organization 1995). Despite that, *O. volvulus* loads are not linearly associated with disease severity, and low and high parasite intensities can result in skin reactions (Ghalib *et al.* 1987; Mukhtar *et al.* 1998; Makunde *et al.* 2000).

Studies on the severity and impact of troublesome itching and OSD began in the 1990s. Qualitative research studies confirmed that OSD and troublesome itching had a negative impact on the mental health and social acceptability of both genders (Brieger *et al.* 1997, 1998a; Vlassoff *et al.* 2000). The burden of illness associated with OSD and itching was higher that expected with Disability Adjusted Life Years (DALYs) lost roughly equivalent to that estimated for ocular disease and blindness (Remme 1998). This finding resulted in an expansion of the ivermectin distribution programme to include communities affected primarily by OSD.

During the period when vector control was the only strategy for control of onchocerciasis, persons already afflicted with onchocercal skin manifestations did not benefit directly from the intervention. Early studies suggested that ivermectin was associated with improvement in severe itching and a decrease in the prevalence and severity of skin lesions (Somo *et al.* 1993; Whitworth *et al.* 1996). In a multicentre trial conducted in Ghana, Nigeria and Uganda, significant reductions in the prevalence and severity of lesions were observed and the prevalence of severe itching was reduced by 40–50% (Brieger *et al.* 1998b; Ogbuagu & Eneanya 1998). Depigmentation

however, is not affected by ivermectin treatment (Pacqué *et al.* 1991b; Burnham 1995; Kennedy *et al.* 2002).

Ectoparasitic infections

Scabies is a highly prevalent infection of the skin caused by infestation with the mite *Sarcoptes scabiei*. The female mite lays her eggs in burrows in the skin, larvae emerge after 2–3 days, they mature, mate, and the process begins again. Infection can cause significant itching and discomfort and scratching can result in secondary bacterial infection by a variety of pathogens including group A *Streptococcus* and *Staphylococcus*. The crusted form of the disease, Norwegian scabies, is characterized by intense infestation and severe symptoms and is typically associated with immune system dysfunction. The prevalence of scabies infection has not been well described, especially in areas of Africa where onchocerciasis is present. However, several reports suggest that the prevalence can exceed 30% in pre-school age children and 6% in older children (Masawe & Nsanzumhgire 1975; Dunne *et al.* 1991; Henderson 1991). Topical agents such as lindane, permethrin, and benzyl benzoate have been the preferred approaches to treatment but these often require multiple applications and have significant side-effects (Green 1989; Wendel & Rompalo 2002). Recently, ivermectin has been shown to be highly effective against both the typical and the crusted forms of scabies (Glaziou *et al.* 1993; Meinking *et al.* 1995; Wendel & Rompalo 2002). An important ancillary benefit to the ivermectin distribution programme is a reduction in the prevalence and severity of scabies in the population. This may also contribute significantly to the acceptability of chemotherapy with ivermectin in these communities.

Infection with head lice caused by *Pediculus humanus humanus* is also a common infection in developing countries. As a part of an ivermectin trial for onchocerciasis in Sierra Leone, Dunne et al. compared the prevalence of head lice in children 5–18 years of age in those receiving ivermectin *vs.* placebo. Receipt of ivermectin was associated with a 46% reduction in the prevalence of head lice (Dunne *et al.* 1991) providing further support to the ancillary ectoparasitic effects of ivermectin.

Intestinal helminth infection

Intestinal helminth infections are widely prevalent in areas endemic for onchocerciasis and throughout the developing world. While ivermectin is ineffective against hookworm and only modestly effective against *Trichuris*, it is highly effective against *Ascaris* infection. *Ascaris* infection, especially high intensity infections, can impair absorption of both macro- and micronutrients and can reduce appetite (Stephenson 2001). The evidence for an impact of deworming on growth and well being of children in the developing world is mixed and depends on the intensity of transmission and reinfection (Dickson *et al.* 2002). In general, there is modest evidence that regular (once or twice yearly) deworming of pre-school age children can lead to modest improvements in weight gain. Little information is available on the effects of reducing the burden of *Ascaris* infection in older children or adults. While only modest effects on growth can be supported by the current literature, recent work for the Global Burden of Disease Project suggests that underweight is the leading risk factor for disability life years (R. Black, personal communication, 2003). Therefore, even modest improvements in weight gain in vulnerable populations may translate into significant improvements in health status of young children. Unfortunately, the current ivermectin distribution programme does not include children under 5 years, the most vulnerable group for growth retardation caused by intestinal helminth infection. Expansion of the age range for dosing with ivermectin to children under 5 years would likely provide significant additional benefits to the population over and above that associated with control of onchocerciasis.

Lymphatic filariasis

More than 1 billion persons are at risk for lymphatic filariasis and over 100 million are infected (Michael *et al.* 1996). This disease is caused by infection with either *Wuchereria bancrofti* or *Brugia malayi*. The complications of these infections are a result of lymphatic obstruction and secondary bacterial infection and include lymphoedema, hydrocele, elephantiasis, and chyluria. Similar to onchocerciasis, much of the tissue damage in lymphatic filariasis is a result of the immune response to the microfilaria and there is no safe and effective macrofilaricide for use in disease control programmes. Both DEC and ivermectin are effective at clearing microfilaria from the blood but do not result in elimination of the infection from individuals (Kazura *et al.* 1993; Das *et al.* 2001). The effectiveness of ivermectin, its safety for use in areas also endemic for onchocerciasis, and its single dose regimen has resulted in significant momentum for using ivermectin as a first-line microfilaricide in filariasis control programmes (Cao *et al.* 1997). In 1997, the WHO called for the elimination of lymphatic filariasis as a global public health problem and established the Global Alliance to Eliminate Lymphatic Filariasis. Following on the success of the MDP for onchocerciasis, Glaxo Smith-Kline announced that it

would donate albendazole to the programme for as long as was necessary. Merck followed this by pledging ivermectin for distribution in combination with albendazole in those countries with coexistent onchocerciasis and lymphatic filariasis. As of 2001, over 17 million doses of ivermectin have been distributed through this programme (World Health Organization 2002). The current target for elimination of lymphatic filariasis is 2020.

Barriers to control programme effectiveness

The achievement and maintenance of onchocerciasis control has been, and continues to be, based on the vigilance, commitment, and participation of all involved and affected by the disease. As with any effort, there are foreseen and unforeseen barriers to the successful achievement of the programme's objectives. Five main barriers of concern are discussed in this section, and their relative importance as an obstacle to the control of onchocerciasis. These are vector and human migration, *Loa loa* coinfection, political instability, drug resistance, and control programme sustainability.

Vector and human migration

The migration of competent, infective blackfly vectors is a substantial threat to the control of onchocerciasis. National borders are insignificant to vectors when suitable habitats for vector propagation are located beyond man-made boundaries. The OCP used aerial larviciding to drastically reduce the blackfly population in a designated area referred to as the 'core', which was eventually freed of *O. volvulus* circulation. When infective blackflies from surrounding regions began to infiltrate, aerial treatment was then extended to the surrounding areas in order to protect the core's 'parasitic insularity' (Hougard *et al.* 2001). Eventually the blackfly populations returned to pre-treatment levels; however, the success of the protection was evident in the continued absence of onchocerciasis from the core area. The prevention of exogenous contamination of *O. volvulus* by infective vectors into parasite-free areas will require novel approaches, and the extension and continuation of mass ivermectin distribution into surrounding endemic areas.

Another impediment to the maintenance of areas containing highly efficient vectors, but free of *O. volvulus*, is human migration from areas still infected with onchocerciasis (De Sole & Remme 1991; Ochoa *et al.* 1997). In order to prevent the intensification of disease and parasite dispersion in such areas, vigilant mass ivermectin treatment is necessary, especially in the absence of vector control. Without appropriate interventions, there is a danger that new foci of active transmission could be formed (Guderian & Shelley 1992).

Loa loa coinfection

Treatment with ivermectin has been shown to significantly decrease *Loa loa* microfilaraemia levels in patients by 90% (Chippaux *et al.* 1998). However, adverse effects, including severe and sometimes fatal encephalopathy, can occur with treatment of persons heavily infected with *Loa loa* (Gardon *et al.* 1997). The use of geographical information systems with effective mapping, modelling and monitoring, can help to delineate areas with high *Loa loa* transmission (Thomson *et al.* 2000). As a result, appropriate precautionary measures prior to ivermectin distribution must be implemented in order to minimize any associated adverse effects. Such measures could include avoidance of communities with high levels of *L. loa* infection or pre-treatment testing of individuals to exclude those with high intensity infections. The optimization of these epidemiological tools may permit the continuation of the safe and effective control of onchocerciasis, and the added benefit of an effective treatment for low intensity *L. loa* infections.

Political instability

Political instability is a considerable obstacle to the implementation and effectiveness of any infectious disease control strategy. Many countries endemic for onchocerciasis are also plagued with political unrest, war, and/or mass displacement of their own or neighbouring citizens. Continuation of control programmes under such conditions requires extreme dedication. Furthermore, sporadic control efforts have limited beneficial impact on the target population. Despite these obstacles, the presence of political instability is not synonymous with the failure of control programmes. In Sudan, a temporary cease-fire was brokered in 1995 during which ivermectin administration occurred, and a water filter programme for the prevention of guinea-worm infection (Homeida *et al.* 1999). Although the efforts were admirable, the resulting coverage of 37% in 1998 was still far below the 65% coverage required to eliminate onchocerciasis as a public health problem (Amazigo *et al.* 2002a). Attempts to continue infectious disease control programs during times of political instability are beneficial to those fortunate enough to be directly affected; however, the achievement of programme goals are significantly hampered and often beyond realization.

Drug resistance

Resistance to ivermectin has been described as unlikely (Taylor & Greene 1989a). Sensitivity tests to ivermectin have been conducted for four different geographical isolates of *O. volvulus*, and their sensitivity was found to

be comparable (Tgaboto *et al.* 1994). Furthermore, only minimal drug resistance has been detected so far in parasites found in veterinary practice. This lack of detectable resistance is important, as these non-human animal parasites have been exposed to ivermectin far longer and with greater intensity than susceptible human parasites. Unfortunately, the current lack of evidence of resistance is not proof of future absence. It has been suggested that there is a strong selective pressure for adults to resume reproduction after ivermectin treatment. Microfilariae produced by such resilient adults could have an increased selective advantage and potentially dominate transmission, leading to hardier macrofilariae (Grant 2000). Thus, routine performance of sensitivity tests in populations with circulating *O. volvulus* strains is crucial, as such tests would allow the rapid identification of developing resistance to ivermectin (Taylor & Greene 1989a).

Programme sustainability

With the conclusion of the Onchocerciasis Control Program, the responsibility for control activities will be absorbed by the countries and the African Program for Onchocerciasis Control. Although countries endemic for onchocerciasis will become more involved in its control, the capacity of countries to assume monitoring and control activities is unequal. The disparity in health policies and infrastructures among these countries will influence the successful integration of control activities into national health systems (Hougard *et al.* 2002). An early obstacle will be the maintenance of enthusiasm of the population during programme development. The programme approach that has met with greatest support is that of community-directed treatment; however, its execution must still be tailored to each country's financial and social capabilities (Amazigo *et al.* 2002b). Furthermore, once a control programme is implemented, its success has been linked to a variety of factors including health education, direct involvement by community members, and community satisfaction with the programme (Shu *et al.* 1999; Katabarwa *et al.* 2002). Thus, the sustainability of onchocerciasis control has formidable obstacles. However, the collaboration of participating countries can yield novel ideas that will assist in the achievement of satisfactory ivermectin coverage, community self-monitoring, and programme cost-recovery.

Conclusions

The discovery of ivermectin as a safe and effective drug for onchocerciasis and the development and operation of the MDP is one of the success stories of public health in the late 20th century. While the impact of the current programme is difficult to measure in absolute terms, it is clear that the direct and indirect benefits of the mass distribution of ivermectin have had a profound impact on the survival and quality of life for many millions of persons living in onchocerciasis endemic areas. Barriers to continued programme success are formidable, but the current approach of involving the communities themselves in the direction and operation of the distribution programme provides strong optimism for future success. Elimination of infection is possible in parts of Central and South America, but continued and aggressive control programme activities will be required in Africa to improve and maintain the benefits already achieved through this pioneering public–private partnership.

References

Abiose A (1998) Onchocercal eye disease and the impact of Mectizan treatment. *Annals of Tropical Medicine and Parasitology* **92** (Suppl. 1), S11–S22.

Albiez EJ, Walter G, Kaiser A *et al.* (1988) Histological examination of onchocercomata after therapy with ivermectin. *Tropical Medicine and Parasitology* **39**, 93–99.

Alley ES, Plaisier AP, Boatin BA *et al.* (1994) The impact of five years of annual ivermectin treatment on skin microfilarial loads in the onchocerciasis focus of Asubende, Ghana. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 581–584.

Amazigo UV, Obono OM, Dadzie KY *et al.* (2002a) Monitoring community-directed treatment programmes for sustainability: lessons from the African Programme for Onchocerciasis Control (APOC). *Annals of Tropical Medicine and Parasitology* **96** (Suppl. 1), S75–S92.

Amazigo UV, Brieger WR, Katabarwa M *et al.* (2002b) The challenges of community-directed treatment with ivermectin (CDTI) within the African Programme for Onchocerciasis Control (APOC). *Annals of Tropical Medicine and Parasitology* **96** (Suppl. 1), S41–S58.

Awadzi K, Dadzie KY, Shulz-Key H, Haddock DRW, Gilles HM & Aziz MA (1985) The chemotherapy of *onchocerciasis. X.* An assessment of four single dose treatment regimes of MK-933 (ivermectin) in human onchocerciasis. *Annals of Tropical Medicine and Parasitology* **79**, 63–78.

Awadzi K, Dadzie KY, Shulz-Key H, Gilles HM, Fulford AJ & Aziz MA (1986) The chemotherapy of onchocerciasis. XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in Northern Ghana. *Annals of Tropical Medicine and Parasitology* **80**, 433–442.

Boatin BA, Hougard JM, Alley ES *et al.* (1998) The impact of Mectizan on the transmission of onchocerciasis. *Annals of Tropical Medicine and Parasitology* **92**, 47–60.

Borsboom GJJM, Boatin BA, Nagelkerke NJD *et al.* (2003) Impact of ivermectin on onchocerciasis transmission assessing the empirical evidence that repeated ivermectin mass treatments

may lead to elimination/eradication in West Africa. *Filaria Journal* **2**, 8.

Boussinesq M, Chippaux JP, Ernould JC, Quillevere D & Prod'hon J (1995) Effect of repeated treatments with ivermectin on the incidence of onchocerciasis in Northern Cameroon. *American Journal of Tropical Medicine and Hygiene* **53**, 63–67.

Brieger WR, Ososanya OO, Kale OO, Oshiname FO & Oke GA (1997) Gender and ethnic differences in onchocercal skin disease in Oyo State, Nigeria. *Tropical Medicine and International Health* **2**, 529–534.

Brieger WR, Ishiname FO & Ososanya OO (1998a) Stigma associated with onchocercal skin disease among those affected near the Ofiki and Oyan rivers in western Nigeria. *Social Science and Medicine* **47**, 841–852.

Brieger WR, Awedoba AK, Eneanya CI *et al.* (1998b) The effects of ivermectin on onchocercal skin disease and severe itching: results of a multicentre trial. *Tropical Medicine and International Health* **3**, 951–961.

Brown KR (1998) Changes in the use profile of Mectizan: 1987–1997. *Annals of Tropical Medicine and Parasitology* **92** (Suppl. 1), S61–S64.

Brown KR & Neu DC (1990) Ivermectin–clinical trials and treatment schedules in onchocerciasis. Review. *Acta Leidensia* **59**, 169–175.

Burnham G (1995) Ivermectin treatment of onchocercal skin lesions: observations from a placebo-controlled, double-blind trial in Malawi. *American Journal of Tropical Medicine and Hygiene* **52**, 270–276.

Cao W, Van der Ploeg CPB, Plaisier AP, Van der Sluijs IJ & Lammie PJ (1997) Ivermectin for the chemotherapy of bancroftian filariasis: a meta-analysis of the effect of single treatment. *Tropical Medicine and International Health* **2**, 393–403.

Chavasse DC, Post RJ, Lemoh PA & Whitworth JAG (1992) The effect of repeated doses of ivermectin on adult female *Onchocerca volvulus* in Sierra Leone. *Tropical Medicine and Parasitology* **43**, 256–262.

Chavasse DC, Post RJ, Davies JB & Whitworth JAG (1993) Absence of sperm from the seminal receptacle of female *Onchocerca volvulus* following multiple doses of ivermectin. *Tropical Medicine and Parasitology* **44**, 155–158.

Chijioke CP & Okonkwo PO (1992) Adverse events following mass ivermectin therapy for onchocerciasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **86**, 284–286.

Chippaux JP, Bouchité B, Boussinesq M, Ranque S, Baldet T & Demanou M (1998) Impact of repeated large scale ivermectin treatments on the transmission of *Loa loa*. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **92**, 454–458.

Cousens SN, Cassels-Brown A, Murdoch I *et al.* (1997) Impact of annual dosing with ivermectin on progression of onchocercal visual field loss. *Bulletin of the World Health Organization* **75**, 229–236.

Cupp EW, Bernardo MJ, Kiszewski AE *et al.* (1986) The effects of ivermectin on transmission of *Onchocerca volvulus*. *Science* **231**, 740–742.

Dadzie KY, Bird AC, Awadzi K, Schulz-Key H, Gilles HM & Aziz MA (1987) Ocular findings in a double-blind study of ivermectin versus diethylcarbamazine versus placebo in the treatment of onchocerciasis. *British Journal of Ophthalmology* **71**, 78–85.

Dadzie KY, Awadzi K, Bird AC & Schulz-Key H (1989a) Ophthalmological results from a placebo controlled comparative 3-dose ivermectin study in the treatment of onchocerciasis. *Tropical Medicine and Parasitology* **40**, 355–360.

Dadzie KY, Remme J, Rolland A & Thylefors B (1989b) Ocular onchocerciasis and intensity of infection in the community. II. West African rainforest foci of the vector *Simulium yahense*. *Tropical Medicine and Parasitology* **40**, 348–354.

Dadzie KY, Remme J, Alley ES & de Sole D (1990) Changes in ocular onchocerciasis four and twelve months after community-based treatment with ivermectin in a holoendemic onchocerciasis focus. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **84**, 103–108.

Dadzie KY, Remme J & De Sole G (1991) Changes in ocular onchocerciasis after two rounds of community based ivermectin treatment in a holo-endemic onchocerciasis focus. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 267–271.

Das PK, Ramaiah KD, Vanamail P *et al.* (2001) Placebo-controlled community trial of four cycles of single-dose diethylcarbamazine or ivermectin against Wuchereria bancrofti infection and transmission in India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **95**, 336–341.

De Sole G & Remme J (1991) Importance of migrants with *Onchocerca volvulus* in west African river valleys protected by 14 to 15 years of *Simulium* control. *Tropical Medicine and Parasitology* **42**, 75–78.

De Sole G, Remme J, Awadzi K *et al.* (1989) Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bulletin of the World Health Organization* **67**, 707–719.

Diallo S, Aziz MA, Lariviere M *et al.* (1986) A double-blind comparison of the efficacy and safety of ivermectin and diethylcarbamazine in a placebo controlled study of Senegalese patients with onchocerciasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **80**, 927–934.

Dickson R, Awasthi S, Demellweek C & Williamson P (2002) Anthelmintic drugs for treating worms in children: effects on growth and cognitive performance (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software, Oxford.

Duke BOL, Zea-Flores G, Castro J, Cupp EW & Muñoz B (1990) Effects of multiple monthly doses of ivermectin on adult *Onchocerca volvulus*. *American Journal of Tropical Medicine and Hygiene* **43**, 657–664.

Duke BOL, Zea-Flores G, Castro J, Cupp EW & Muñoz B (1991) Comparison of the effects of a single dose and of four six-monthly doses of ivermectin on adult *Onchocerca volvulus*. *American Journal of Tropical Medicine and Hygiene* **45**, 132–137.

Duke BOL, Zea-Flores G, Castro J, Cupp EW & Muñoz B (1992) Effects of three-month doses of ivermectin on adult *Onchocerca volvulus*. *American Journal of Tropical Medicine and Hygiene* **46**, 189–194.

Dunne CL, Malone CJ & Whitworth JAG (1991) A field study of the effects of ivermectin on ectoparasites of man. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 550–551.

Gardon J, Gardon-Wendel N, Demanga-Ngangue, Kamgno J, Chippaux JP & Boussinesq M (1997) Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. *Lancet* **350**, 18–22.

Gardon J, Boussinesq M, Kamgno J, Gardon-Wendel N, Demanga-Ngangue & Duke BOL (2002) Effects of standard and high doses of ivermectin on adult worms of *Onchocerca volvulus*: a randomized control trial. *Lancet* **360**, 203–210.

Ghalib HW, Mackenzie CD, Kron MA, Williams JF, El Khalifa M & El Sheikh H (1987) Severe onchocercal dermatitis in the Ethiopian border region of Sudan. *Annals of Tropical Medicine and Parasitology* **81**, 405–419.

Glaziou P, Cartel JL, Alzieu P, Briot C, Moulia-Pelat JP & Vartin PMV (1993) Comparison of ivermectin and benzyl benzoate for treatment of scabies. *Tropical Medicine and Parasitology* **44**, 331–332.

Grant W (2000) What is the real target for ivermectin resistance selection in *Onchocerca volvulus*? *Parasitology Today* **16**, 458–459.

Green MS (1989) Epidemiology of scabies. *Epidemiologic Reviews* **11**, 126–150.

Greene BM, Taylor HR, Cupp EW *et al.* (1985) Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *New England Journal of Medicine* **313**, 133–138.

Guderian RH & Shelley AJ (1992) Onchocerciasis in Ecuador: the situation in 1989. *Memorias do Instituto Oswaldo Cruz* **87**, 405–415.

Guzzo CA, Furtek CI, Porras AG *et al.* (2002) Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *Journal of Clinical Pharmacology* **42**, 1122–1133.

Henderson C (1991) Community control of scabies (letter). *Lancet* **337**, 1548.

Hoerauf A, Volkmann L, Hamelmann C *et al.* (2000) Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet* **355**, 1242–1243.

Hoerauf A, Mand S, Adjei O, Fleischer B & Büttner DW (2001) Depletion of Wolbachia endobacteria in *Onchocerca volvulus* by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* **357**, 1415–1416.

Homeida MMA, Goepp I, Ali M, Hilyer E & Mackenzie CD (1999) Medical achievements under civil war conditions. *Lancet* **354**, 601.

Hougard JM, Alley ES, Yaméogo L, Dadzie KY & Boatin BA (2001) Eliminating onchocerciasis after 14 years of vector control: a proved strategy. *Journal of Infectious Diseases* **184**, 497–503.

Hougard JM, Yameogo L & Philippon B (2002) Onchocerciasis in West Africa after 2002: a challenge to take up. *Parasite* **9**, 105–111.

Katabarwa MN, Habomugisha P & Richards FO Jr (2002) Implementing community-directed treatment with ivermectin for the control of onchocerciasis in Uganda (1997–2000): an evaluation. *Annals of Tropical Medicine and Parasitology* **96**, 61–73.

Kazura J, Greenberg J, Perry R, Weil G, Day K & Alpers M (1993) Comparison of single-dose diethymcarbamizine and ivermectin for treatment of bancroftian filariasis in Papua New Guinea. *American Journal of Tropical Medicine and Hygiene* **49**, 804–811.

Kennedy MH, Bertocchi I, Hopkins AD & Meredith SE (2002) The effect of 5 years of annual treatment with ivermectin (Mectizane®) on the prevalence and morbidity of onchocerciasis in the village of Gami in the Central African Republic. *Annals of Tropical Medicine and Parasitology* **96**, 297–307.

Kläger SL, Whitworth JAG & Downham MD (1996) Viability and fertility of adult *Onchocerca volvulus* after 6 years of treatment with ivermectin. *Tropical Medicine and International Health* **1**, 581–589.

Lariviere M, Vingtain P, Aziz M *et al.* (1985) Double-blind study of ivermectin and diethylcarbamazine in African onchocerciasis patients with ocular involvement. *Lancet* **2**, 174–177.

Makunde WH, Salum FM, Massaga JJ & Alilio MS (2000) Clinical and parasitological aspects of itching caused by onchocerciasis in Morogoro, Tanzania. *Annals of Tropical Medicine and Parasitology* **94**, 793–799.

Masawe AEJ & Nsanzumhgire H (1975) Scabies and other skin diseases in preschool children in Ujamma villages in Tanzania. *Tropical and Geographic Medicine* **27**, 288–294.

Meinking TL, Taplin D, Hermida JL, Pardo R & Kerdel FA (1995) The treatment of scabies with ivermectin. *New England Journal of Medicine* **333**, 26–30.

Michael E, Bendy DAP & Grenfell BT (1996) Reassessing the global prevalence and distribution of lymphatic filariasis. *Parasitology* **112**, 409–428.

Molyneux DH (1995) Onchocerciasis control in West Africa: current status and future of the onchocerciasis control programme. *Parasitology Today* **11**, 399–402.

Mukhtar MM, Khier MM, Baraka OZ & Homeida MMA (1998) The burden of *Onchocerca volvulus* in Sudan. *Annals of Tropical Medicine and Parasitology* **92** (Suppl. 1), S129–S131.

Njoo FL, Belling GAC, Oosting J, Vetter JCM, Stilma JS & Kijlstra A (1993) Concurrent parasitic infections in onchocerciasis and the occurrence of adverse reactions after ivermectin treatment. *American Journal of Tropical Medicine and Hygiene* **48**, 652–657.

Ochoa JO, Castro JC, Barrios VM, Juarez EL & Tada I (1997) Successful control of onchocerciasis in San Vincente Pacaya, Guatemala,1984–1989. *Annals of Tropical Medicine and Parasitology* **91**, 471–479.

Ogbuagu KF & Eneanya CI (1998) The multi-centre study of the effect of mectizan treatment on onchocercal skin disease: clinical findings. *Annals of Tropical Medicine and Parasitology* **92** (Suppl. 1), S139–S145.

Pacque MC, Dukuly Z, Greene BM *et al.* (1989) Community-based treatment of onchocerciasis with ivermectin: acceptability and early reactions. *Bulletin of the World Health Organization* **67**, 721–730.

Pacqué M, Muñoz B, Poetschke G, Foose J, Greene BM & Taylor HR (1990a) Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* **336**, 1486–1489.

Pacqué M, Muñoz B, Greene BM *et al.* (1990b) Safety of and compliance with community-based ivermectin therapy. *Lancet* **335**, 1377–1380.

Pacqué M, Muñoz B, Greene BM & Taylor HR (1991a) Community-based treatment of onchocerciasis with ivermectin: safety, efficacy, and acceptability of yearly treatment. *Journal of Infectious Diseases* **163**, 381–385.

Pacqué M, Elmets C, Dukuly Z *et al.* (1991b) Improvement in severe onchocercal skin disease after a single dose of ivermectin. *American Journal of Medicine* **90**, 590–594.

Plaisier AP, Alley ES, van Oortmarssen GJ, Boatin BA & Habbema JDF (1997) Required duration of combined annual ivermectin treatment and vector control in the Onchocerciasis Control Programme in West Africa. *Bulletin of the World Health Organization* **75**, 237–245.

Prod'hon J, Lardeux F, Bain O, Hébrard G & Prud'hom JM (1987) Ivermectine et modalités de la réduction de l'infection des Simulies dans un foyer forestier d'onchocercose humaine. *Annales de Parasitologie Humaine et Comparee* **62**, 590–598.

Remme JHF (1998) Onchocerciasis. In: *The global epidemiology of infectious diseases* (eds CJL Murray & A Lopez) Harvard University Press, Cambridge.

Remme J, Baker RHA, De Sole G *et al.* (1989) A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. I. Effect of the microfilarial reservoir and the transmission of *Onchocerca volvulus*. *Tropical Medicine and Parasitology* **40**, 367–374.

Remme J, DeSole G, Dadzie KY *et al.* (1990) Large scale ivermectin distribution and its epidemiological consequences. *Acta Leidensia* **59**, 177–191.

Rothova A, Van Der Lelij A, Stilma JS, Wilson WR & Barbe RF (1989) Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* **1**, 1439–1441.

Saint André AV, Blackwell NM, Hall LR *et al.* (2002) The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindness. *Science* **295**, 1892–1895.

Shu EN, Nwadike KI, Onwujekwe EO, Ugwu OC & Okonkwo PO (1999) Influence of health education on community participation in rapid assessment of onchocerciasis prior to distribution of ivermectin. *East African Medical Journal* **76**, 320–323.

Somo RM, Ngosso A, Dinga JS, Enyong PA & Fobi G (1993) A community-based trial of ivermectin for onchocerciasis control in the forest of southwestern Cameroon: clinical and parasitologic findings after three treatments. *American Journal of Tropical Medicine and Hygiene* **48**, 9–13.

Stephenson LS (2001) Optimising the benefits of anthelmintic treatment in children. *Paediatric Drugs* **3**, 495–508.

Taylor HR & Greene BM (1989a) The status of ivermectin in the treatment of human onchocerciasis. *American Journal of Tropical Medicine and Hygiene* **41**, 460–466.

Taylor MJ & Hoerauf A (1999) *Wolbachia* bacteria of filarial nematodes. *Parasitology Today* **15**, 437–442.

Taylor HR, Semba RD, Newland HS *et al.* (1989b) Ivermectin treatment of patients with severe ocular onchocerciasis. *American Journal of Tropical Medicine and Hygiene* **40**, 494–500.

Taylor HR, Pacqué M, Muñoz B & Greene BM (1990) Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. *Science* **250**, 116–118.

Tchakoute VL, Bronsvoort M, Tanya V, Renz A & Trees AJ (1999) Chemoprophylaxis of *Onchocerca* infections: in a controlled, prospective study ivermectin prevents calves becoming infected with *O. ochengi*. *Parasitology* **118**, 195–199.

Tgaboto SK, Townson S, Titanji VPK, Awadzi K, Castro J & Zea-Flores G (1994) Comparison of the sensitivity of different geographical isolates of *Onchocerca volvulus* microfilariae to ivermectin: effects of exposure to drug on development in the blackfly *Simulium ornatum*. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 237–241.

Thomson MC, Obsomer V, Dunne M, Connor SJ & Molyneux DH (2000) Satellite mapping of *Loa loa* prevalence in relation to ivermectin use in west and central Africa. *Lancet* **356**, 1077–1078.

Trpis M, Childs JE, Fryauff DJ *et al.* (1990) Effect of mass treatment of a human population with ivermectin on transmission of *Onchocerca volvulus* by *Simulium yahense* in Liberia, West Africa. *American Journal of Tropical Medicine and Hygiene* **42**, 148–156.

Vlassoff C, Weiss M, Ovuga EBL *et al.* (2000) Gender and the stigma of onchocercal skin disease in Africa. *Social Science and Medicine* **50**, 1353–1368.

Wendel K & Rompalo A (2002) Scabies and pediculosis pubis: an update of treatment regimens and general review. *Clinical Infectious Diseases* **35** (Suppl. 2), S146–S151.

White AT, Newland HS, Taylor HR *et al.* (1987) Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. *Journal of Infectious Diseases* **156**, 463–470.

Whitworth JAG, Gilbert CE, Mabey DM, Maude GH, Morgan D & Taylor DW (1991) Effects of repeated doses of ivermectin on ocular onchocerciasis: community based trial in Sierra Leone. *Lancet* **338**, 1100–1103.

Whitworth JAG, Morgan D, Maude GH, Luty AJF & Taylor DW (1992) A community trial of ivermectin for onchocerciasis in Sierra Leone: clinical and parasitological responses to four doses given at six-monthly intervals. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **86**, 277–280.

Whitworth JAG, Maude GH & Downham MD (1996) Clinical and parasitological responses after up to 6.5 years of ivermectin treatment for onchocerciasis. *Tropical Medicine and International Health* **1**, 786–793.

Winnen M, Plaisier AP, Alley ES *et al.* (2002) Can ivermectin mass treatments eliminate onchocerciasis in Africa? *Bulletin of the World Health Organization* **80**, 384–390.

World Health Organization (1995) *The importance of onchocercal skin disease; report of the Pan-African study group on*

onchocercal skin disease. Document TDR/AFR/RP/95.1. WHO, Geneva.

World Health Organization (2002) *Annual Report on Lymphatic Filariasis*. Document WHO/CDS/CPE/CEE/2002.28. WHO, Geneva.

Zea-Flores R, Richards FO Jr, González-Peralta C *et al.* (1992) Adverse reactions after community treatment of onchocerciasis with ivermectin in Guatemala. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **86**, 663–666.

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