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The impact and cost of ivermectin control strategies against River Blindness in Africa

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November 2013

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Submitted in part fulfilment of the requirements for the degree of
Doctor of Philosophy in Infectious Disease Epidemiology of Imperial College London

Abstract

River Blindness (onchocerciasis) has been identified by the World Health Organization as potentially eliminable. Until recently, the African Programme for Onchocerciasis Control focused on annual distribution of ivermectin to reduce morbidity, but encouraged by success in some foci, it has embarked on eliminating the infection from the continent. To this end, increasing the treatment frequency to twice yearly (biannual) has been suggested. However, this may not be cost-effective everywhere in Africa, so it is necessary to assess under which epidemiological scenarios it would be advisable. The central aim of this thesis is to develop further an onchocerciasis transmission model (EpiOncho) to evaluate the impact and cost of biannual vs. annual ivermectin treatment in a range of scenarios typical of savannah onchocerciasis foci in Africa.

The analyses and methods are divided into three main components. First, a mathematical model of the dynamics of onchocercal disease was developed and linked to infection output from EpiOncho. Results indicate that although long-term annual ivermectin treatment reduces dramatically onchocerciasis related disease burden, its overall impact on infection depends strongly on baseline levels of endemicity.

Second, a study was conducted in Ghana to assess the economic cost of biannual relative to annual ivermectin distribution. Results indicate that the (per year) cost of biannual ivermectin treatment is approximately 60% higher than that of annual treatment (and not simply double, as assumed by others).

Third, the health impact, programmatic cost, and projected duration of biannual vs. annual ivermectin treatment were evaluated. Findings indicate that although biannual treatment yields only small additional health benefits over those of annual treatment, its benefit is pronounced in the context of elimination goals, shortening timeframes to reach proposed operational thresholds for stopping treatment and potentially generating programmatic cost savings. Notwithstanding these conclusions, the feasibility of increasing from one to two treatments yearly will vary with the specific programmatic circumstances.

Contents

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Declaration of Own Work

All ideas presented within this thesis were formulated by the candidate under the guidance of Professor María-Gloria Basáñez, Dr Thomas S Churcher, Dr Martin Walker and Professor Roger K Prichard. All sources used in this thesis have been cited appropriately. I would like to acknowledge Dr Mike Y Osei-Atweneboana's, Mr Edward J Tettevi's, Mr Odame Asiedu's, and Dr Nana-Kwadwo Biritwum's assistance in the collection of the cost data (presented in Chapter 4). The following papers were published (or under review at the time of examination (14/3/2014)) during this PhD:

- Turner, H.C., Churcher, T.S., Walker, M., Prichard, R.K., Osei-Atweneboana, M.Y. and Basáñez, M-G. (2013) Uncertainty surrounding projections of the long term impact of ivermectin treatment on human onchocerciasis. *PLoS Negl Trop Dis,* 7(4): e2169
- Turner, H.C., Osei-Atweneboana, M.Y., Walker, M., Tettevi, E.J., Churcher, T.S. Asiedu, O., Biritwum, N-K. and Basáñez, M-G (2013). The cost of annual versus biannual community-directed treatment of onchocerciasis with ivermectin: Ghana as a case study. *PLoS Negl Trop Dis,* 7(9): e2452
- Turner, H.C., Walker, M., Churcher, T.S. and Basáñez, M-G. Modelling the impact of ivermectin on River Blindness and its burden of morbidity and mortality in African savannah: EpiOncho projections. *Under Review*
- Turner, H.C., Walker, M., Churcher, T.S., Osei-Atweneboana, M.Y., Biritwum, N-K., Hopkins, A., Prichard, R.K. and Basáñez, M-G. Reaching the London Declaration on Neglected Tropical Diseases for onchocerciasis: an economic evaluation of increasing the frequency of ivermectin treatment in Africa. *Under Review*

For all of these papers, the candidate conducted the analyses and wrote the first draft.

Signed: 

Hugo Turner

Acknowledgements

I would like to thank my supervisors Professor María-Gloria Basáñez, Dr Thomas Churcher, and Professor Roger Prichard for their support, guidance and expertise.

I would also like to thank Dr Mike Osei-Atweneboana, Mr Edward Tettevi, Mr Odame Asiedu, and Dr Nana-Kwadwo Biritwum for their assistance with my field work in Ghana, Dr Adrian Hopkins from the Mectizan Donation Program (MDP) and Dr Martin Walker for his support throughout my PhD.

I would like to thank the Economic and Social Research Council (ESRC) for my PhD studentship.

Finally I would like to thank my friends and family who have supported and encouraged me.

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Glossary

Annual biting rate: the average number of *Simulium* bites to which a person is exposed during a whole year.

Annual transmission potential: the average number of infective larvae (L3) of *Onchocerca volvulus* potentially received during a whole year by a person exposed to the annual biting rate.

Anti-macrofilarial action: a cumulative adverse effect on adult worm reproductive fitness / longevity (represented in the model as a per dose reduction in the per capita rate of microfilarial production by adult female worms).

Community microfilarial load (CMFL): the geometric mean number of microfilariae per skin snip among adults aged 20 years and above.

Cost-Effectiveness analysis: a form of economic analysis that compares the relative costs and outcomes (effects) of two or more courses of action.

Density dependence: the dependence upon population density of the per capita rate at which a demographic or biological process occurs.

Deterministic model: a model which describes what happens on average in a population and does not incorporate the effects of chance.

Disability adjusted life years: a time-based measure of disease burden accounting for years of life lost due to premature mortality and healthy years of life lost due to disability.

Doxycycline: a tetracycline antibiotic which targets the *Wolbachia* endosymbiotic bacteria of *Onchocerca volvulus* which are vital for development of incoming L3 larvae to adult stages, adult worm fertility, and parasite survival.

Economic costs: also include, in addition to financial costs, estimates of the monetary value of goods or services for which no financial transaction has taken place.

Embryostatic: the effect of a drug which impedes microfilarial production by adult female worms.

Financial costs: are those where a monetary transaction has taken place for the purchase of a resource.

Internal rate of return: the discount rate applied to the (monetary) benefits and costs of control programmes, that sets the net present value (NPV – the difference between the former and latter) to zero. If it is greater than the market interest rate (or the cost of borrowing money) the programme is considered to be an economically worthy investment.

Ivermectin (Mectizan®): a macrocyclic lactone widely used in the field of veterinary medicine against a wide range of parasitic nematodes. The drug has been used extensively in onchocerciasis control strategies and has both microfilaricidal and embryostatic effects.

Macrofilaricidal: the effect of a drug which increases adult worm mortality.

Microfilaricidal: the effect of a drug which increases microfilarial mortality.

Microfilaridermia: presence of microfilaria in the skin

Microsimulation: a type of simulation modelling that generates individual life histories (i.e. explicitly models each individual)

Moxidectin: a drug under clinical assessment by a WHO-based project called MACROFIL, which has been established to develop a macrofilaricidal drug to treat onchocerciasis.

Net present value (NPV): the difference between the discounted present value of the control programme benefits (such as the monetary benefit of preventing blindness cases) and the discounted present value of the control programme costs (such as the costs of treatment).

Operational Thresholds for Treatment Interruption followed by Surveillance (OTTIS): Based on experiences in foci in Mali and Senegal (Diawara *et al.* 2009; Tekle *et al.* 2012), cessation of onchocerciasis control in the OCP and ONCHOSIM projections, the African Programme for Onchocerciasis Control has set operational thresholds for treatment interruption followed by Surveillance (OTTIS). Namely, these are a microfilarial prevalence (by skin snipping) <5% in all surveyed villages and <1% in 90% of such villages, and <0.5 infective larvae per 1,000 flies (African Programme for Onchocerciasis Control, 2010).

Rapid epidemiological mapping of ochocerciasis (REMO): a mapping technique utilising nodule palpation of a sample of adult males aged 20 and above to determine village level prevalence of onchocerciasis.

Stochastic model: a model which incorporates the effects of chance (i.e. random process).

Systematic non-complier: someone who is eligible for treatment but who never takes / receives it.

Therapeutic coverage: proportion of the total population receiving ivermectin at each round.

Transmission breakpoints: the threshold below which the parasite population is not able to maintain itself.

Acronyms and Abbreviations

ABR: Annual biting rate

APOC: The African Programme for Onchocerciasis Control

ATP: Annual transmission potential

CDD: Community drug distributor

CDTI: Community directed treatment with ivermectin

CMFL: Community microfilarial load

DALYs: Disability adjusted life years

ESRC: Economic and Social Research Council

GABA: Gamma-aminobutyric acid

GHC: Ghana cedi

GHS: Ghana Health Service

GluCls: Glutamate-gated-Cl-channels

GNI: Gross national income

IRR: Internal rate of return

LDNTD: London Declaration on Neglected Tropical Diseases

MDA: Mass drug administration

MDP: Mectizan Donation Program

Mf: Microfilariae

mg: Milligram

NBD: Negative binomial distribution

NGO: Non-governmental organization

NPV: Net present value

NTD: Neglected tropical disease

NTDP: Neglected Tropical Disease Programme

OCP: Onchocerciasis Control Programme in West Africa

OEPA: Onchocerciasis Elimination Program for the Americas

OTTIS: Operational thresholds for treatment interruption followed by surveillance

PAHO: Pan American Health Organization

REMO: Rapid epidemiological mapping of onchocerciasis

RHS: Right hand side

s.l.: Sensu lato

s.str.: Sensu stricto

SAEs: Severe adverse events

WHO: World Health Organization

YLD: Years lived with disability

YLL: Years of life lost

Chapter 1: General Introduction

1.1. Introduction

Human onchocerciasis is a neglected tropical disease (NTD) mainly affecting the eyes and the skin. It is caused by the parasitic filarial nematode *Onchocerca volvulus* and is transmitted by the bites of *Simulium* blackflies (Duke, 1990). Onchocerciasis is often referred to as River Blindness due to the high prevalence of eye disease in villages located along fast flowing rivers where the blackfly vectors breed. With at least 37 million people infected and a further 120 million at risk, it is the second largest cause of infectious blindness (Basáñez *et al.* 2006; World Health Organization, 1995). Onchocerciasis also causes disfiguring skin lesions and severe dermal itching that can drastically impair individuals' quality of life, and lead to stigmatisation (Brieger *et al.* 1998a; Vlassoff *et al.* 2000). Of those at risk, 99% live in Africa; however, the disease is also endemic in six countries of Latin America in smaller circumscribed foci and in Yemen (Duke, 1990).

During the last 30 years there has been a rapid and remarkable expansion of onchocerciasis control programmes worldwide (Etya'ale, 2001). These programmes have made a large impact on reducing onchocerciasis as a public health problem, initially using only large scale vector control (initiated in West Africa in 1975) and followed by the widespread annual distribution of ivermectin (mostly initiated in the early 1990's). Recently, there has been a shift in onchocerciasis control policy in Africa, with the aim of programmes' changing from morbidity control to elimination of infection (London Declaration on Neglected Tropical Diseases, 2013; World Bank, 2012). However, the feasibility of achieving this new goal with annual ivermectin distribution alone, and the cost-effectiveness of potential alternatives, such as increasing the frequency of ivermectin distribution to twice a year are unknown.

1.2. Life Cycle and Epidemiology

Onchocerca volvulus developmental cycle (Figure 1.1) comprises long-lived adult worms (macrofilariae) living in subcutaneous nodules which have an average female reproductive

life span of approximately ten years; the embryonic skin-dwelling microfilariae (Mf), with a mean life expectancy of 12-24 months); larvae which develop (L1 to L3) within the fly in approximately one week and attain infectivity to humans (these stages do not reproduce or multiply within the vector) and immature stages (L4 and juvenile adults) that reach sexual maturity in the human host and start producing detectable Mf after approximately two years (Basáñez & Boussinesq, 1999; Duke, 1991; Duke, 1993; Plaisier *et al.* 1991). Humans are the definitive host for the parasite and there is no animal reservoir (Bradley *et al.* 2005). Many stages of *O. volvulus* life cycle (both within the vector and human hosts) are influenced by density-dependent processes (i.e. are regulated by the density of the parasite population) (Basáñez *et al.* 2002; Basáñez *et al.* 1995; Basáñez & Ricardez-Esquinca, 2001; Basáñez *et al.* 1996).

The epidemiological patterns of onchocerciasis, and in particular the prevalence of ocular disease, vary considerably between geographical zones (Duke *et al.* 1966). For instance, while onchocercal associated blindness can be found at a very high prevalence (over 10%) in hyperendemic communities in the savannah regions, generally less blindness is found in forest foci with a similar intensity of infection (Cheke & Garms, 2013; Dadzie *et al.* 1989; Prost, 1980a). It has been hypothesized that this difference is due to the existence of various *O. volvulus* strains of different pathogenicity. Support for this hypothesis has been provided by DNA-based identification, which has confirmed an association between savannah and forest parasite types with severe and mild ocular onchocerciasis respectively (Zimmerman *et al.* 1992). More recently, a higher concentration of the endosymbiotic *Wolbachia* bacteria in *O. volvulus* (which have been proposed to be a contributory factor to inflammatory disease (Brattig, 2004; Saint Andre *et al.* 2002)) has been reported in the savannah than in forest parasites (Higazi *et al.* 2005). Though generally forest regions do not have a high prevalence of blindness, onchocercal associated skin disease is still an important public health problem in these regions (Remme, 2004a; World Health Organization, 1995).

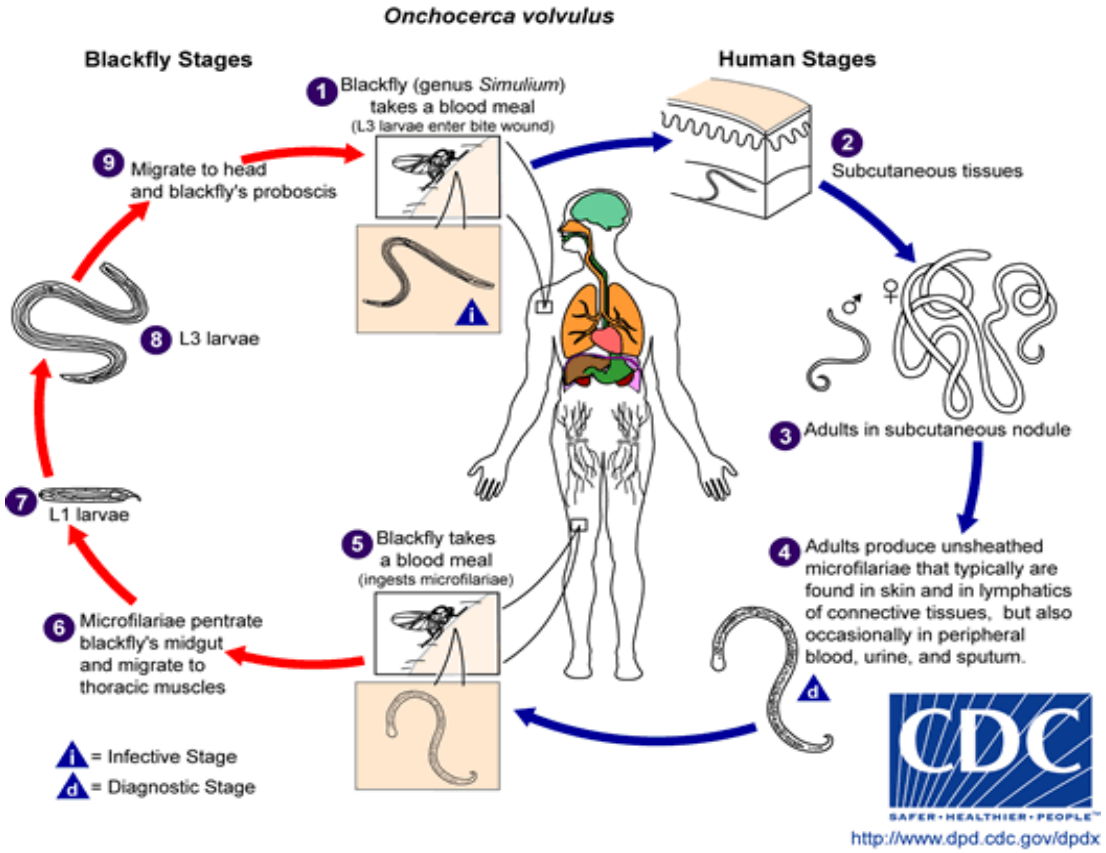

Figure 1.1. The Life Cycle of *Onchocerca volvulus*. *The adult worms live in nodules under the skin. Reproducing adult females shed between 500 to 1500 microfilariae (Mf) per day, (Schulz-Key, 1990), which migrate to the skin and eyes where they cause the pathology related to the disease. Blackflies serve as the vector of the parasite and ingest Mf from the skin when they bite an infectious person. The Mf can then mature into L3 larvae in approximately a week (extrinsic incubation period) and become infectious to humans. Then, when the fly bites a human the larvae will enter the human host and develop into adulthood. When the adults (male and female macrofilariae) mate they will produce more Mf completing the transmission cycle (Bradley et al. 2005). Figure adapted from CDC (http://www.cdc.gov/parasites/onchocerciasis/biology.html).*

In addition, age-specific patterns of *O. volvulus* infection show strong variation according to location, and host sex (Filipe *et al.* 2005). Several possible explanations have been suggested including; age- and sex-specific exposure to vectors, endocrine factors, and parasite-induced immunosuppression (Duerr *et al.* 2003; Filipe *et al.* 2005). These patterns have implications for our understanding of *O. volvulus* population biology and the design of control strategies. A summary of the definitions of endemicity are shown in Table 1.1.

Table 1.1. Endemicity categories as defined by microfilarial prevalence.

Endemicity	Microfilarial prevalence
Hypoendemic	Under 35%
Mesoendemic	35% to 60%
Hyperendemic	Over 60%
Highly hyperendemic	Over 80%

Table adapted from (Prost *et al.* 1979).

1.2.1. Vectors

Onchocerciasis is transmitted by blackflies (genus *Simulium)* which breed in swift running water, such as streams and rivers as their eggs require well oxygenated water to mature to larval and pupal stages (Crosskey, 1990). Female blackflies require a blood meal to produce eggs, and it is during this meal that they may transmit or receive the onchocercal infection (the male flies never suck blood) (Crosskey, 1990). The flies only bite during the day (Bradley *et al.* 2005).

Many blackfly (Diptera: Simuliidae) species are capable of transmitting onchocerciasis; however, species differ in their intrinsic ability to transmit the infection and their degree of anthropophagy (their propensity to feed on humans), and this contributes to the diverse transmission patterns across different endemic areas. In Africa, members of the *Simulium damnosum sensu lato* (s.l.) species complex (which includes approximately 60 cytoforms), and *Simulium neavei* are important vectors (Crosskey, 1990; Crosskey & Howard, 2004; Leake, 1993). It has been estimated that members of the *S. damnosum* complex are responsible for over 90% of onchocerciasis cases worldwide and more than 95% of cases in Africa (Crosskey, 1990). In Latin America, *S. ochraceum s.l.*, *S. exiguum s.l.*, *S. metallicum s.l.*, and *S. guianense s.l.* are the main vectors (Basáñez *et al.* 2006). Certain species of blackflies, particularly in Latin America, have a cibarial armature (a chitinous tooth like projection) which damage Mf as they are ingested. This has important implications for the density-dependent processes operating within these vectors (Basáñez & Ricardez-Esquinca, 2001).

1.3. Disease

Onchocerciasis is the second largest cause of infectious blindness and was thought to be responsible for at least 270,000 cases of blindness with another 500,000 people suffering from severe visual impairment (Basáñez *et al.* 2006; World Health Organization, 1995). Recently these estimates have been revised upwards to 340,000 cases of blindness and 645,000 people suffering from severe visual impairment (Coffeng *et al.* 2010).

1.3.1. Pathology

Most of the Mf do not reach a blackfly vector and instead die in the human body, provoking an inflammatory reaction due to the host's immune system reacting around dead or moribund Mf. Blindness is caused by a progressive accumulation of this process when Mf invade the eye tissues, which leads to irreversible ocular lesions (via a progression through punctuate keratitis; sclerosing keratitis; corneal opacities, optic nerve atrophy), resulting first in visual impairment and eventually total blindness (Remme *et al.* 2006). Blindness incidence has been shown to be associated with past Mf load, supporting the progressive worsening of onchocerciasis associated blindness with parasite exposure (Little *et al.* 2004a). A novel hypothesis has proposed that in addition to the Mf antigens, the pro-inflammatory responses are also triggered by the endosymbiotic *Wolbachia* bacteria (released by dying Mf) (Brattig, 2004; Saint Andre *et al.* 2002).

Onchocerciasis also causes troublesome itching and (disfiguring) skin changes, including early-stage reactive lesions, and late-stage depigmentation (leopard skin), and atrophy (Murdoch *et al.* 1993). Most patients (even those with a high skin Mf load) present with subclinical or intermittent dermatitis (Pearlman *et al.* 1999). Like the visual pathology, the inflammation appears to be largely induced by the endosymbiotic *Wolbachia* bacteria (Brattig, 2004). Patients can develop more severe or hyperreactive skin lesions due to repeated cycles of inflammation, eosinophil and macrophage infiltration and destruction of Mf (Ali *et al.* 2003). The varied immune responses to the parasite and subsequent clinical presentation may be influenced by host genetic factors (Meyer *et al.* 1994).

It should also be noted that Mf can invade many tissues / organs and that onchocerciasis can also be a systemic disease that is associated with musculoskeletal pain and reduced body

mass index (Bradley *et al.* 2005). Involvement of heavy Mf infection is also suspected in the onset of epilepsy (Boussinesq *et al.* 2002; Pion *et al.* 2009) and a hyposexual dwarfism syndrome (Nakalanga syndrome) (Kipp *et al.* 1996; Newell *et al.* 1997). In addition individuals suffering from onchocercal related vision loss and sighted individuals with high microfilaridermia have a notable additional risk of mortality (Kirkwood *et al.* 1983; Little *et al.* 2004b; Pion *et al.* 2002; Walker *et al.* 2012).

1.4. Socioeconomic Consequences

In addition to causing disease and excess mortality, onchocerciasis also causes tremendous social and economic damage. Though the public health importance of onchocercal associated blindness has long been recognized, only in 1995 did research demonstrate the importance of onchocercal associated skin disease (Remme *et al.* 2006; World Health Organization, 1995). The troublesome itching caused by the skin disease makes working, studying, and interacting socially difficult (Brieger *et al.* 1998a; Murdoch *et al.* 2002; Vlassoff *et al.* 2000). In addition, the disease also reduces marriage prospects, affects self-esteem, decreases concentration and leads to a loss of earnings in infected individuals as a result of both decreased productivity and increased spending on additional health costs (Amazigo, 1994; Kim *et al.* 1997). For example a study by Kim *et al*. (1997) found that workers with onchocercal associated skin disease lost an average of 1.9 days of work per month.

On a community level, the disease can also hinder economic growth, as when the onchocercal associated blindness prevalence reaches high levels, too few able-bodied individuals are left to work (Amazigo *et al.* 2006). Food shortages and economic collapse can force residents to abandon fertile land and move to highlands and forested areas where there is poor soil, water shortages and overcrowding (Amazigo *et al.* 2006). In West Africa the disease led to people abandoning more than 25 million hectares of arable land (Levine, 2007). Consequently the disease is considered to directly retard development and aggravate poverty (Levine, 2007).

1.5. Onchocerciasis Control

In the past vector control was the only feasible intervention for onchocerciasis because until the end of the 1980's, the only available drugs (suramin, diethylcarbamazine), were too toxic for large-scale use. Weekly applications of larvicidal insecticides in the breeding sites effectively stopped local vector breeding and in some cases led to local elimination of the vectors; however, the programmes could not prevent reinvasion of infective vectors from other areas (Remme *et al.* 2006).

Because blackflies migrate across international borders, it was decided that vector control should be carried out in the form of a large-scale regional programme in the West African savannah (Remme *et al.* 2006). This led to the creation of the Onchocerciasis Control Programme in West Africa (OCP), in 1974.

1.5.1. The Onchocerciasis Control Programme in West Africa (OCP)

The OCP was launched in 1974, with the goal of eliminating River Blindness as a disease of public health importance (Richards *et al.* 2001). The OCP originally covered seven countries, namely, Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, Niger and Togo (Richards *et al.* 2001). However, by 1986 the OCP had expanded its operations to include four more countries: Guinea, Guinea Bissau, Senegal and Sierra Leone (this is known as the western extension of the OCP) (Richards *et al.* 2001). When the programme ended in 2002, it covered 11 countries (Figure 1.2), an area of 1,300,000 km^2 and an estimated population of over 78 million (Boatin, 2008; Richards *et al.* 2001).

Figure 1.2. A map of Africa, showing the areas covered by the African Programme for Onchocerciasis Control (APOC;) and the Onchocerciasis Control Programme (OCP;).
Figure taken from (Boatin, 2008).

From 1974 to 1988 the OCP relied on a strategy of weekly aerial larviciding of blackfly breeding sites (supplemented when feasible with ground larviciding) (Richards *et al.* 2001). The OCP initially used temephos, an affordable and efficient organophosphorous insecticide which had little impact on non-target organisms (Richards *et al.* 2001). Subsequently the OCP used a rotation of seven larvicides to reduce the emergence of insecticide resistance (Richards *et al.* 2001). Due to the long life expectancy (ten years) of the adult worm, to achieve total interruption of parasite transmission the operations were anticipated to run

approximately 20 years (Davies *et al.* 1978; Plaisier *et al.* 1991). However, although this strategy reduced transmission and infection (Hougard *et al.* 2001), other than preventing an infection from getting worse, it had no direct benefit for already diseased individuals and was not considered feasible or cost-effective elsewhere in Africa (Diawara *et al.* 2009).

In 1987 ivermectin was registered for human use against onchocerciasis (having been developed, as with most anthelmintics, for veterinary infections), and due to the suitability of this drug for mass treatment (excluding children under 5 years, pregnant women and those breastfeeding a child under one week old), large scale chemotherapeutic control programmes became feasible (Richards *et al.* 2001). The mathematical models used at the time projected that ivermectin distribution in combination with the on-going vector control would shorten the duration of required larviciding (Plaisier *et al.* 1997). Large scale mass drug administration (MDA) of ivermectin began in the OCP regions in 1989, initially administered by mobile teams, and became an important component of the control strategy, both as a complement to larviciding and in some of the western extension regions, as a sole intervention (Boatin, 2008).

Benefits and achievements:

The OCP is considered a tremendously successful programme (with the exception of Sierra Leone, where operations were interrupted by a decade long civil war) (Boatin & Richards, 2006). The following are considered some of the key benefits (Remme *et al.* 2006; Richards *et al.* 2001):

- Over 40 million people in the participating countries are now considered free from infection and eye lesions.
- Approximately 600,000 cases of blindness have been prevented.

In addition, the OCP had a dramatic socioeconomic impact; 25 million hectares of land were freed from onchocerciasis and were made available for resettlement and agriculture, leading to an estimated US$3.7 billion in increased labour and agricultural productivity in the participating countries (Richards *et al.* 2001).

Many of the former OCP countries now have integrated onchocerciasis control into their own national health systems.

1.5.2. The African Programme for Onchocerciasis Control (APOC)

The African Programme for Onchocerciasis control (APOC) was launched in 1995 and targeted the 19 onchocerciasis endemic countries in Africa that were not covered by the OCP (though three of them, Kenya, Rwanda, and Mozambique, were found not to be endemic), protecting an at risk population of 120 million (Basáñez *et al.* 2006; Remme, 1995). The goal of APOC was to eliminate onchocerciasis as a disease of public health and socio-economic importance in the non-OCP countries. The strategy to achieve this goal was by establishing effective and sustainable, annual mass ivermectin treatment to all those aged 5 years and older (excluding pregnant women and those breastfeeding a child under one week old) (Basáñez *et al.* 2006). The programme, initially conceived to end in 2007 (Richards *et al.* 2001), and subsequently in 2015 (World Health Organization, 2010), has recently been extended until 2025 with the new goal and commitment for the elimination of onchocerciasis (World Bank, 2012).

Unlike the OCP, which was a vertical programme and had limited local participation, the APOC has been integrated within the national health systems of the participating countries (Tsalikis, 1993).

Ivermectin is provided through a community directed treatment strategy, which is thought to empower the local populations, as they are making the key decisions. It is believed that community directed treatment with ivermectin (CDTI) strengthens the health systems of the participating countries (ensuring high coverage) and it is being used as a platform for integrating other community-based interventions (Basáñez *et al.* 2006; Richards *et al.* 2001).

The APOC also utilizes a rapid field assessment process known as REMO (Rapid Epidemiological Mapping of Onchocerciasis) to define the high-risk areas (Ngoumou *et al.* 1994).

Benefits and achievements:
The APOC is also deemed to be a successful programme and the following are considered some of its key benefits and achievements to date (World Health Organization, no date; Basáñez *et al.* 2006; Richards *et al.* 2001)

- Approximately one million disability adjusted life years (DALYs) per year are saved.

- Other health interventions are co-implemented with CDTI (such as the distribution of bednets).
- The prevalence of troublesome itching related to onchocerciasis was reduced by 68% between 1995 and 2008 (8.9 million cases prevented).
- Prevents over 40,000 blindness cases every year.
- An estimated 7.5 million years of productive labour will have been added.

1.5.3. The Onchocerciasis Elimination Program for the Americas (OEPA)

Although onchocerciasis is most prevalent in Africa, it also occurs in 13 discrete foci across six countries of the Americas: Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela (Sauerbrey, 2008). However, in many areas the annual transmission potentials (ATPs) are considerably lower than those observed in Africa (though this observation does not apply to all areas – see Basáñez *et al.* (2002)). It has been proposed that these lower ATP values are due to lower vector competence and vectorial capacity of the simuliid species prevailing in some foci (Basáñez *et al.* 2009).

Establishment of new foci via human migration does not occur often and the New World vectors do not fly large distances (Basáñez *et al.* 2000). Therefore, the foci are stable and are susceptible to a focused control programme (perhaps with the exception of the Amazonian focus straddling Venezuela and Brazil, where transmission patterns are complex, and afflicted populations are small and isolated in a remote yet vast region) (Grillet *et al.* 2008). In the remaining foci, it is anticipated that if the programmes are maintained in these targeted and relatively circumscribed areas for 10–15 years, the adult parasite population will not be able to replenish itself and will become locally eliminated. The mass ivermectin treatment programmes could then be halted without fear of recrudescence.

Noting this opportunity, in 1991 the directing council of the Pan American Health Organization (PAHO) made a resolution to eliminate onchocerciasis as a public health problem in the Americas by 2007 (Sauerbrey, 2008). This led to the creation of the Onchocerciasis Elimination Program for the Americas (OEPA) in 1992 (Sauerbrey, 2008). The elimination strategy is based on the biannual (twice a year) distribution of ivermectin, to all endemic communities (covering at least 85% of the eligible population). A biannual

distribution strategy was used because several studies have indicated that, by decreasing the interval between ivermectin treatments, it is possible to keep Mf levels low enough to suppress parasite transmission (particularly in those areas where local vectors possess cibarial armatures – see section 1.2.1)) (Cupp *et al.* 1986; Cupp *et al.* 1989; Cupp *et al.* 1992).

Benefits and Achievements:
As of 2013, a total of 11 of the 13 endemic foci in the Americas have interrupted transmission and there has been no incident blindness cases associated with onchocerciasis reported (Centers for Disease Control and Prevention, 2013). Furthermore, in July 2013, Colombia publicly announced it had become the first country in the Americas to become verified as having eliminated River Blindness (Carter Center, 2013).

1.6. Ivermectin (Mectizan®)

In 1982 researchers at Merck & Co discovered that a new antiparasitic agent that was used to treat gastrointestinal worms in veterinary medicine, was also effective against *O. volvulus* (Aziz *et al.* 1982). Clinical trials in Africa sponsored by Merck & Co and the WHO demonstrated that annual ivermectin treatment was safe (permitting MDA), prevented ocular and dermal morbidity, and significantly reduced transmission (Remme, 2004b). In 1987, Merck & Co took the unprecedented decision to donate ivermectin for as long as needed to eliminate onchocerciasis as a public health problem (Basáñez *et al.* 2006). The standard dose of ivermectin is 150-200 μg per kilogram of body weight (Gardon *et al.* 2002).

Ivermectin is a potent microfilaricide causing over a 90% reduction in skin Mf load within a few days, and a maximum reduction of 98-99% approximately two months after treatment (Basáñez *et al.* 2008). This delay in maximum effect can be explained by observations that ivermectin causes Mf to migrate from the sub-epidermal layer into deeper dermis layers, where they are killed by the hosts immune system (Knab *et al.* 1997; Wildenburg *et al.* 1994). A meta-analysis and mathematical modelling study performed by Basáñez *et al*. (2008) indicates that the placebo-corrected microfilaricidal efficacy of ivermectin is between 92–99%.

Ivermectin also has an embryostatic effect on adult female worms, temporally blocking the release of Mf (Alley *et al.* 1994; Plaisier *et al.* 1995). The estimated efficacy of this embryostatic effect is approximately 70%, with the maximum reduction reached one to two months after treatment (Basáñez *et al.* 2008). However, recuperation of adult worm fertility occurs slowly from three to four months after treatment onwards (Basáñez *et al.* 2008; Duke *et al.* 1991a).

When given in a single dose, ivermectin has shown no evidence of a macrofilaricidal effect (killing of adult worms) (Albiez *et al.* 1988; Schulz-Key *et al.* 1985). However, when administered at high frequencies (such as monthly intervals) ivermectin has a small (but statistically significant) macrofilaricidal effect (Duke *et al.* 1990). It has also been reported that when administered for prolonged periods (over many years) ivermectin may have an cumulative adverse effect on adult worm reproductive fitness / longevity (i.e. an anti-macrofilarial action, not necessarily killing the worms but reducing their reproductive fitness / lifespan), perhaps inducing changes in intranodular sex ratios and decreasing insemination rates (Chavasse *et al.* 1993; Cupp *et al.* 2004; Cupp *et al.* 2011; Duke, 2005; Duke *et al.* 1991b; Plaisier *et al.* 1995; Tekle *et al.* 2012; Whitworth *et al.* 1996a). However, there is considerable uncertainty regarding the magnitude of this potential anti-macrofilarial action. The modelling analysis by Plaisier *et al*. (1995), suggested that annual ivermectin reduces adult worm fertility irreversibly by 30-35% with each treatment round i.e. ivermectin has a large cumulative impact on adult worms microfilarial production. However, the modelling analysis by Bottomley *et al*. (2008), did not find evidence for a strong cumulative effect on microfilarial production. Furthermore, a recent epidemiological evaluation in Cameroon by Pion *et al.* (2013) does not support the operation of a strong cumulative effect of repeated ivermectin treatments on the microfilarial productivity of female worms.

1.6.1. Mode of action

Ivermectin was originally believed to act primarily by opening gamma-aminobutyric acid (GABA) gated channels in invertebrate neurons / muscle cells, leading to hyperpolarisation of the cells and to an inhibitory paralysis (Campbell, 1985; Dourmishev *et al.* 2005). Though, later evidence indicates that the drug's primary effect is on glutamate-gated Cl-channels (GluCls), a previously unrecognised class of ligand-gated channels (Cully *et al.* 1994).

However, very little is known about how ivermectin inhibits reproduction in *O. volvulus* and whether this effect is mediated by opening of GABA-gated and GluCls channels or due to the drug being highly lipophilic (Prichard, 2007). It has been proposed that ivermectin's microfilaricidal effect is due to opening of a GluCl channel that is expressed in the secretory pore cells, leading to the suppression of the ability of the Mf to secrete proteins that enable evasion of the host immune system (based on work on *Brugia malayi*) (Moreno *et al.* 2010).

1.6.2. Adverse reactions and severe adverse effects

A standard dose of ivermectin treatment in humans is generally well tolerated. This is in marked contrast with the two previously available drugs for the treatment of onchocerciasis, diethylcarbamazine and suramin, which were frequently associated with severe side effects (Taylor *et al.* 1989). Chijioke and Okonkwo, (1989) found that 97% of the reported adverse events associated with ivermectin were mild and did not stop the patient from attending work. Common side effects include oedema, headache and a worsening of rash (Chijioke and Okonkwo, 1989). The incidence of adverse effects has been found to be directly related to skin microfilarial load and was highest in the foci with the highest endemicity levels (De Sole *et al.* 1989).

In addition, several cases of severe adverse events (SAEs) such as encephalitis, neurologic disorders, coma and death post-ivermectin treatment have been reported in some patients infected with heavy burdens of *Loa loa* (Boussinesq *et al.* 2003; Boussinesq *et al.* 1998), another filarial nematode prevalent in forested areas of central Africa. Currently it is recommended that in areas where the *L.loa* microfilarial prevalence is above a threshold of 20% there is an unacceptable risk of SAEs and ivermectin is not distributed (Boussinesq *et al.* 2001).

1.6.3 Sub-optimal responses to ivermectin treatment

In Ghana, studies have reported sub-optimal responses to ivermectin treatment, where individual hosts were found to harbour a higher than expected Mf load after several rounds of ivermectin treatment (in comparison with other individuals treated the same number of times who were deemed to be good responders) (Awadzi *et al.* 2004a; Awadzi *et al.* 2004b). These studies by Awadzi and colleagues controlled for a number of factors including age, weight,

general health and the timing / number of treatments but were conducted on a relatively small number of individuals in a clinical setting.

Subsequently, Osei-Atweneboana *et al*. (2007) conducted a more extensive epidemiological study, covering a number of regions in Ghana, and taking samples at various time points (before and after treatment). The results indicate that the observed higher levels of skin Mf, were not due to the loss of ivermectin's microfilaricidal efficacy, but more likely due to the adult female worms resuming reproductive activity earlier than expected in individuals responding well to treatment. Further investigation of these areas has revealed that there were very few young worms in the poor responding communities, indicating that the results were not due to reinfection (Osei-Atweneboana *et al.* 2011). This suggests that the adult worms could be becoming resistant to the embryostatic effect of ivermectin.

This reduction in ivermectin's effectiveness could be happening in other areas of West Africa, but there is a lack of data from other countries in the region (Osei-Atweneboana *et al.* 2007). There have also been reports of sub-optimal responses to ivermectin in Sudan although reduced immune responsiveness in some of the cases has been suggested as a possible explanation (Ali *et al.* 2002).

1.7. Alternative Drugs

1.7.1. Anti-Wolbachia therapies

A recent approach for treating onchocerciasis targets the *Wolbachia* endosymbionts of *O. volvulus,* which are vital for development of incoming L3 larvae to adult stages, adult worm fertility, and parasite survival. *Wolbachia* are maternally inherited alpha proteobacteria and have been found in numerous arthropod species and filarial nematodes (including *O. volvulus and Wuchereria bancrofti*). *Wolbachia* bacteria have been shown to be susceptible to tetracycline and rifampicin antibiotics (Fenollar *et al.* 2003). Thus far human trials have focused on the use of doxycycline and have found that a 6-week course results in the long-term depletion of *Wolbachia*, leading to long-lasting inhibition of embryogenesis and sustained reductions in Mf (Hoerauf *et al.* 2001; Hoerauf *et al.* 2003; Hoerauf *et al.*

2008). Doxycycline also retards the development of *O. volvulus* larvae (L1-L3) as Mf depleted of *Wolbachia* develop poorly (Wanji *et al.* 2009).

An important advantage of anti-*Wolbachia* therapies is that they can be given safely to people co-infected with *L. loa,* as this parasite does not have the bacteria and is therefore unaffected by this treatment (Wanji *et al.* 2009). Doxycycline cannot be given to pregnant women (or those who are breastfeeding) and children under 9 years of age (Wanji *et al.* 2009).

A trial by Wanji *et al*. (2009) indicates that a distribution strategy that uses community health implementers and directly observed treatment can be a successful way of distributing doxycycline with high compliance. This suggests that administration of doxycycline could be a successful strategy in several situations, such as the control of onchocerciasis in areas of co-endemicity with loiasis, areas where ivermectin resistance may be suspected / sub-optimal responses have been reported, and to mop-up activities in areas close to elimination (Taylor *et al.* 2009). However, given the prolonged duration of treatment (daily for 6 weeks), this is reliant on coverage and compliance staying at high levels and a shorter treatment course may be required before this strategy is adopted by control programmes at a large scale.

1.7.2. Moxidectin

Moxidectin is a macrocyclic lactone and a highly efficacious microfilaricide (Cotreau *et al.* 2003). Like ivermectin it has been used as an ingredient in deworming agents used in veterinary medicine (Etya'ale, 2001).

A WHO based project called MACROFIL which has been established to develop a macrofilaricidal drug to treat onchocerciasis, had identified moxidectin as a potential candidate (Etya'ale, 2001). On July 1, 2009, WHO announced a phase III trial designed to compare the efficacy of moxidectin relative to that of ivermectin. However, it is important to note that moxidectin is not currently licenced for humans.

1.7.3. Flubendazole

Flubendazole is a potent and efficacious anthelmintic for gastrointestinal nematode infections in domestic animals. In a number of experimental filarial rodent models prolonged administration of flubendazole was found to have essentially a 100% efficacy as a

macrofilaricide (Mackenzie & Geary, 2011). A trial for human onchocerciasis was carried out in Mexico in the 1980's (Dominguez-Vazquez *et al.* 1983) which had promising results. However, wider testing in humans was restricted, due to problems associated with the route of administration (via intramuscular injection) (Mackenzie & Geary, 2011). Currently efforts are under way to reformulate flubendazole so that it can be administered orally to provide a long half-life, required for anti-filarial activity.

1.8. Cost of the Programmes

The financial cost of the OCP (from 1975–2002) was approximately US$570 million (provided by donors) (Remme *et al.* 2006). APOC (from 1995 –2015) has been projected to cost US$478 million – excluding economic costs (such as the donated ivermectin tablets) (Coffeng *et al.* 2013). The costs of the further extension to 2025 have not been estimated. OEPA cost US$10 million between 1991-2003 (Remme *et al.* 2006), and it has been supported by The Carter Center.

A cost-benefit analysis has estimated the net present value (NPV– see glossary) for the OCP over a 39 year project horizon (1974 to 2012), to range from US$3.7 billion to US$485 million depending on the discount rate assumed (values shown are for 3% and 10%, respectively) (Kim & Benton, 1995). These values correspond to an internal rate of return (IRR– see glossary) of approximately 20%, which is due mainly to increased labour productivity and increased land use (a IRR above 10% is considered by the World Bank as the standard for successful public health programme) (Kim & Benton, 1995). This value is consistent with other cost-benefit analysis of the OCP such as Benton & Skinner (1990) who estimated a minimum IRR of 11-13% and Haddix (1997) who estimated an IRR of 24%. A similar cost-benefit analysis was performed for APOC by the World Bank, which found that the programme IRR (for 1996 through 2017) was 17% (Benton, 1998). These studies are summarized in more detail in Waters *et al.* (2004).

However, many of the cost-benefit analyses for onchocerciasis control do not account for the benefit attributable to the reduction in onchocercal associated skin disease and consequently may notably underestimate the control programmes benefits.

It is noteworthy that a recent modelling study by Coffeng *et al.* (2013) has estimated that APOC costs US$27 per DALY averted, and is therefore considered highly cost-effective. However, there are very few other analyses systematically evaluating the cost-effectiveness of onchocerciasis control.

1.9. Prospects of Onchocerciasis Elimination in Africa

Recent epidemiological and entomological evaluations conducted in Mali and Senegal suggest that 15-17 years of annual (or biannual) ivermectin distribution (in the absence of vector control) may be sufficient to lead to local onchocerciasis elimination in certain foci (Diawara *et al.* 2009; Traore *et al.* 2012). In addition, local elimination may also have been achieved with 15–17 years of annual ivermectin distribution in 26 villages in Kaduna state, Nigeria (the first report of such evidence for the APOC operational area) (Tekle *et al.* 2012). These studies have provided proof of principle that elimination with annual ivermectin distribution may be feasible in some African foci. In 2009, an international expert group convened to discuss the implications of these results (African Programme for Onchocerciasis Control, 2010). Based on experiences with cessation of onchocerciasis control in West Africa, and ONCHOSIM projections, the group developed an operational framework for elimination and provisionally defined operational thresholds for treatment interruption followed by surveillance (OTTIS), namely, a microfilarial prevalence below 5% in all surveyed villages (and below 1% in 90% of the villages), and a proportion of local simuliid vectors harbouring < 0.5 L3 larvae per 1,000 flies (African Programme for Onchocerciasis Control, 2010).

Spurred by the documented success in the Mali, Nigeria, and Senegal foci (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012), there has recently been a shift in onchocerciasis control policy in Africa, with the aim changing from morbidity control to elimination of infection. For instance the APOC has a new goal of elimination of onchocerciasis where possible by 2025 (World Bank, 2012), and the London Declaration on Neglected Tropical Diseases (LDNTD), on 31 January 2012, joined the World Health Organization's (WHO) 2020 Roadmap on NTDs (London Declaration on Neglected Tropical Diseases, 2013) and set goals for elimination of onchocerciasis in selected countries of Africa by 2020 (World Health

Organization, 2013). The feasibility of reaching these goals, is supported by the results of ONCHOSIM, a microsimulation model for onchocerciasis transmission, which have indicated that elimination of onchocerciasis from most endemic foci in Africa is possible with annual ivermectin distribution at a high coverage (African Programme for Onchocerciasis Control 2010) – the transmission models and their projections are discussed in more detail in Chapter 2.

However, based on Plaisier *et al*. (1995), the ONCHOSIM model projections have assumed that ivermectin has a large cumulative impact on female adult worm fertility (a large anti-macrofilarial action). However, as discussed in section 1.6, this may not be the case (Bottomley *et al.* 2008; Pion *et al.* 2013). Furthermore, the foci where elimination has been reported had a low pre-control endemicity and strongly seasonal transmission. Consequently, the conclusions regarding the feasibility of elimination with annual ivermectin distribution alone cannot necessarily be generalised to other areas (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012). Additionally, a review assessing the impact of repeated ivermectin MDA in the former OCP area indicated that long term annual ivermectin treatment is unlikely, on its own, to lead to the elimination of transmission of onchocerciasis from West Africa (Borsboom *et al.* 2003); though it would likely lead to the elimination (or near elimination) of its public health burden.

1.10. Rationale

Although onchocerciasis elimination has been reported in some African foci (with a low pre-control endemicity) the feasibility of the current elimination goals, with annual ivermectin distribution alone remains uncertain. Recently, increasing the treatment frequency to twice a year in some African foci has come under consideration. This has been shown in Latin America to have the potential to interrupt transmission (Gonzalez *et al.* 2009; Rodriguez-Perez *et al.* 2010). However, it is unknown in what ecological and programmatic circumstances this strategy may be advisable in Africa. It should be noted that a biannual ivermectin distribution strategy was used in one of the three Mali and Senegal foci investigated by Diawara *et al.* (2009) (described in section 1.9), and was reported to show no clear advantage over annual treatment; as it took a similar number of years to reach

elimination as the other two foci using annual treatment (Diawara *et al.* 2009). However, it was acknowledged that the study design did not determine exactly when the "elimination threshold" was reached, and it is possible that it was achieved several years earlier in the foci that used biannual treatment (Diawara *et al.* 2009). Furthermore the pre-control endemicity level in the foci that used biannual treatment (River Gambia) was notably higher than the other two foci which treated annually (River Bakoye and River Faleme); (only 3 of the 39 (8%) villages in the foci treated annually were hyperendemic compared to 9 of 22 (40%) of the villages in the foci treated biannually (De Sole *et al.* 1993; De Sole *et al.* 1991; Diawara *et al.* 2009) (when defining hyperendemic as in Table 1.1). Therefore these foci are not directly comparable, making it difficult to make accurate conclusions regarding the benefit of biannual treatment. In this regard, mathematical models of the dynamics onchocerciasis transmission can be a useful tool to investigate the potential benefit of a biannual treatment strategy.

1.11. Research Aims and Thesis Structure

The central aim of this thesis is to further develop a sex- and age-structured deterministic onchocerciasis transmission model (EpiOncho) (Churcher & Basanez, 2009; Filipe *et al.* 2005), to evaluate the impact of biannual versus annual ivermectin distribution in a range of endemic, economic and programmatic scenarios typical of savannah onchocerciasis foci in Africa. The specific aims and principal findings of the analyses are summarised before each chapter and so only a brief synopsis is given here.

In Chapter 2, EpiOncho is described, and further developed to incorporate treatment compliance and account for the potential cumulative effect of ivermectin on adult worm fertility (section 1.6). The implications of the assumption that ivermectin has a large anti-macrofilarial action, as assumed in the current elimination projections using ONCHOSIM was explored.

In Chapter 3, a mathematical model of the dynamics of onchocercal disease was developed, by linking ocular and skin morbidity, as well as excess mortality to infection output from

EpiOncho. This was used to investigate the impact of long term ivermectin control on disease and infection in different ecological and programmatic scenarios.

In Chapter 4, a study was conducted in Ghana to assess the economic cost of biannual relative to annual ivermectin distribution.

In Chapter 5, the health impact, programmatic cost, and projected duration of biannual vs. annual ivermectin treatment were evaluated in a range of endemic, economic and programmatic scenarios typical of savannah onchocerciasis foci in Africa.

In the concluding chapter (Chapter 6) the wider implications of the work are considered with particular reference to the potential policy implications. Future applications of the model are also discussed. In order to facilitate reading, the various chapters focus on the general methods and discussion of the results, leaving the mathematical detail to the corresponding supplementary materials located at the end of the relevant chapters.

Chapter 2: Uncertainty Surrounding Current the Onchocerciasis Elimination Projections

2.1. Summary

Recently, and spurred by the documented success in several foci (in Mali, Nigeria, and Senegal) there has been a shift in onchocerciasis control policy in Africa, with the aim of programmes changing from morbidity control to elimination of infection. The feasibility of achieving these goals is supported by the projections of ONCHOSIM (a microsimulation model for onchocerciasis transmission). However, these model projections are assuming that ivermecitn has a strong cumulative impact on microfilarial production (i.e. a large anti-macrofilarial action), which several studies have indicated may not be the case. In this Chapter, a deterministic onchocerciasis transmission model (EpiOncho) was modified to explore how assumptions regarding: a) treatment effects on microfilarial production by female worms (fertility),and b) treatment coverage and compliance, effect the long term impact of annual and biannual ivermectin treatment on microfilarial load and prevalence in a highly endemic African savannah setting. It was found that if ivermectin does not have a large anti-macrofilarial action, elimination of onchocerciasis in highly endemic areas of Africa may not be feasible with annual ivermectin distribution alone. Furthermore assumptions regarding the proportion of systematic non-compliers (those who never taking treatment), were found to be just as influential as those for overall coverage when projecting the long-term impact of ivermectin distribution.

A modified version of this chapter has been is published: Turner, H.C., Churcher, T.S., Walker, M., Prichard, R.K., Osei-Atweneboana, M.Y. and Basáñez, M-G. (2013) Uncertainty surrounding projections of the long term impact of ivermectin treatment on human onchocerciasis. PLoS Negl Trop Dis 7: e2169. (See Appendix A)

2.2. Introduction

Recent epidemiological and entomological evaluations conducted in Mali, Nigeria, and Senegal have shown that ivermectin distribution on its own may, in some foci, lead to local elimination of onchocerciasis (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012). These results have paved the way towards considering that it may be possible, in certain foci in Africa, to eliminate onchocerciasis using ivermectin.

2.2.1. ONCHOSIM projections

ONCHOSIM is a computer program for modelling the transmission and control of onchocerciasis which was developed in collaboration with the Onchocerciasis Control Programme in West Africa (OCP) and the Department of Public Health of the Erasmus University, Rotterdam. The model uses stochastic microsimulation to calculate the life events of individual persons and inhabitant parasites, and a deterministic simulation of the dynamics of the *Simulium* population and the development of the parasite in the flies (Plaisier *et al.* 1990). See Habbema *et al.* (1996) and Plaisier *et al.* (1990) for a more detailed description of the model. ONCHOSIM has been used to investigate the impact of different control strategies such as chemotherapy with ivermectin (with and without concomitant vector control) and has recently been used to predict the duration of annual ivermectin distribution required for elimination in Africa (African Programme for Onchocerciasis Control, 2010; Plaisier *et al.* 1997; Winnen *et al.* 2002). The results indicated that elimination of onchocerciasis from most endemic foci in Africa is possible with a high coverage of annual ivermectin distribution (Table 2.1).

Table 2.1. ONCHOSIM's predicted probability of onchocerciasis elimination in relation to pre-control endemicity levels

Pre-control intensity (CMFL)	Number of years of annual treatment							
	65% overall coverage				80% overall coverage			
	10 yrs	15 yrs	20 yrs	25 yrs	10 yrs	15 yrs	20 yrs	25 yrs
10 Mf per skin snip	95%	100%	100%	100%	100%	100%	100%	100%
30 Mf per skin snip	4%	89%	100%	100%	40%	100%	100%	100%
50 Mf per skin snip	0%	12%	82%	99%	0%	68%	100%	100%
70 Mf per skin snip	0%	0%	19%	75%	0%	11%	85%	99%

CMFL: community microfilarial load, Mf: microfilariae. Table adapted from African Programme for Onchocerciasis Control (2010).

In these modelling projections, the overall therapeutic treatment coverage was varied as part of the sensitivity analysis (African Programme for Onchocerciasis Control, 2010), however, the potential influence of different levels of systematic non-compliers (the proportion of the eligible population who never take treatment) on the feasibility of elimination was not independently investigated. Furthermore, as mentioned in the previous chapter, a crucial conjecture of these projections was that adult female worms, after temporarily ceasing microfilarial production due to the embryostatic effect of ivermectin, gradually reach a new production level which is reduced irreversibly by an average of 30-35% after each treatment round (Plaisier *et al.* 1995), effectively assuming a strong cumulative effect of ivermectin on microfilarial production. This is equivalent to an increasing proportion of worms not contributing to transmission i.e. a strong anti-macrofilarial action (a cumulative adverse effect on adult worm reproductive fitness / longevity).

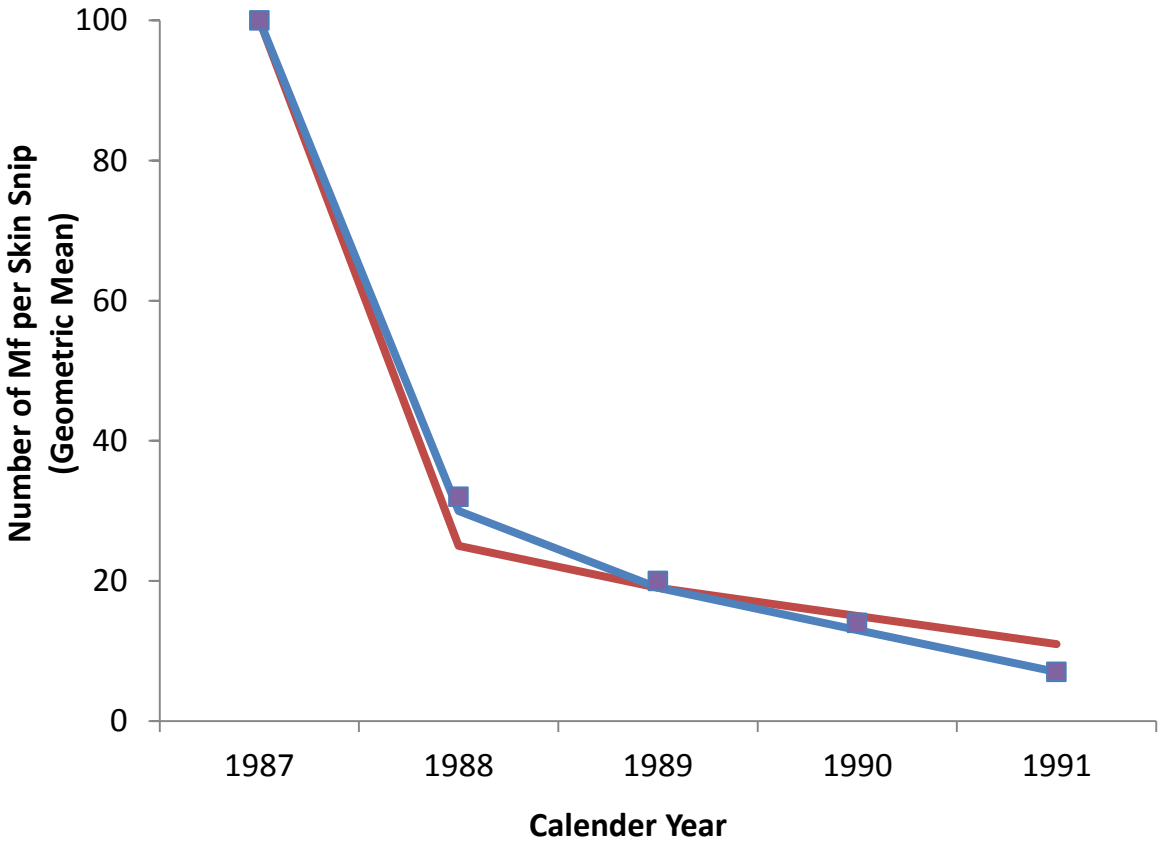

Figure 2.1. ONCHOSIM projections fitted to Asubende trial data under two different proposed effects of ivermectin on *Onchocerca volvulus* microfilarial production. *The markers represent the trial data (Alley et al. 1994). The red line represents model projections assuming no cumulative impact on microfilarial productivity and the blue assuming a 35% cumulative reduction after each treatment. This figure was reproduced from Plaisier et al. (1995).*

The data that informed the model in Plaisier *et al.* (1995) comprised longitudinal microfilarial load follow up, from 74 individuals who all received five annual ivermectin doses in a community trial in Asubende, Ghana (Alley *et al.* 1994). Figure 2.1. contrasts two model fits by Plaisier *et al.* (1995) to the five mean (geometric) annual microfilarial counts from Alley *et al.* (1994). The two hypotheses being tested to explain the observed trend are a null hypothesis of all ivermectin-exposed adult worms regaining their full microfilarial productivity vs. an alternative hypothesis of a 35% reduction in productivity with each treatment round. The authors of Plaisier *et al.* (1995) concluded that the model assuming the alternative hypothesis provided a better fit to the data. However, given that:

a) the microfilarial loads were measured per skin snip instead of per mg of skin; however, the weight of a skin snip sample can range between 0.5 and 3 mg (and lighter snips are more likely yield a false negative result),

b) microfilarial counts originated from snips incubated for only 30 minutes in distilled water (Prost & Prod'hon, 1978) (which is likely to underestimate the microfilarial load as microfilaridermia decreases),

there is the possibility of considerable measurement error (Walker *et al.* 2012). This is particularly important regarding the last two data points in the dataset (the most influential for discriminating between the two hypotheses – see Figure 2.1.). Furthermore for the last two years of the community trial in Asubende, the study area was receiving vector control in addition to ivermectin, potentially making it difficult to disentangle the effects of treatment from those of antivectorial measures. However the authors of Plaisier *et al.* (1995) indicate that the impact of vector control was taken into account in their model.

Another modelling study, using data from a community trial with five biannual treatment rounds in Guatemala (Collins *et al.* 1992), did not find evidence for a cumulative effect on microfilarial production (Bottomley *et al.* 2008).This study followed 510 individuals (7 times as many as Alley *et al.* (1994)), who took all five 6-monthly doses of ivermectin from 1988 to 1990 in the absence of vector control in Guatemala, with microfilarial loads measured per mg of skin after 24 hours incubation (Collins *et al.* 1992). In addition a recent epidemiological evaluation in Cameroon (Pion *et al.* 2013), found a similar distribution of microfilarial densities after ivermectin treatment from a group of communities that had been under ivermectin control for 13 years (with the number of ivermectin doses received ranging between 5 and 24), compared to a group of communities from an endemic area with no previous history of large-scale treatments. Observing similar response profiles in these two groups of communities after ivermectin treatment does not support the operation of a strong cumulative effect of repeated treatments on the microfilarial productivity of female worms.

Whether or not ivermectin has a strong cumulative effect on microfilarial production (a large anti-macrofilarial action) will have important implications for the optimal design of mass drug administration (MDA) programmes, and given the sparse data that exist, this issue

represents an area of considerable uncertainty which needs to be taken into account in modelling studies estimating the long-term impact of ivermectin treatment.

In this Chapter, a deterministic onchocerciasis transmission model (EpiOncho) (Basáñez & Boussinesq, 1999; Basáñez *et al.* 2008; Churcher & Basáñez, 2008; Filipe *et al.* 2005) is modified to explore the uncertainty in modelling projections of the long-term impact of ivermectin on *Onchocerca volvulus* populations due to assumptions concerning: a) strong cumulative impact on microfilarial production (i.e. a large anti-macrofilarial action), and b) treatment coverage and compliance. How these affect the benefit of annual vs. biannual treatment frequency was also explored.

2.3. Method

2.3.1. EpiOncho

EpiOncho is a sex- and age-structured deterministic onchocerciasis transmission model (Churcher & Basanez, 2009; Filipe *et al.* 2005), which describes the rate of change with respect to time and host age of the mean (arithmetic) number of fertile and non-fertile adult worms per host, the mean (arithmetic) number of microfilariae (Mf) per mg of skin (Mf/mg), and the mean (arithmetic) number of larvae per fly. The equations and model parameters are described in section 2.8 presented at the end of the chapter.

Human age- and sex-structure reflects the demography in savannah areas of northern Cameroon (Anderson *et al.* 1974; Filipe *et al.* 2005; Renz *et al.* 1987), as it is in savannah areas of Africa that the prevailing *O. volvulus– Simulium damnosum* combinations are responsible for the most severe sequelae of onchocerciasis (Basáñez *et al.* 2006; Bradley *et al.* 2005; Duke, 1990). Parameters for vector competence, survival, and host choice were those for savannah species of the *S. damnosum sensu lato* (s.l.) complex (*S. damnosum sensu stricto* (s. str.)/and *S. sirbanum*) (Basáñez *et al.* 2009; Filipe *et al.* 2005), responsible for onchocerciasis transmission in the region (Duke *et al.* 1975; Renz & Wenk, 1987).

The annual biting rate (ABR) by blackfly vectors was set to 37,300 bites per person per year (well within the range of values recorded in savannah areas (Duke *et al.* 1975; Renz & Wenk, 1987; Schulz-Key *et al.* 1985)), to achieve a baseline mean (arithmetic) microfilarial load of

36 Mf/mg across all ages in the population, (which corresponds to a mean (arithmetic) microfilarial load of 60 Mf/mg of skin in those aged 20 years and above). Note that the mean microfilarial load per mg of skin in those aged ≥ 20 years here is an arithmetic mean, not a geometric mean of the number of Mf per skin snip in the same age group, known as the community microfilarial load (CMFL) (Remme *et al.* 1986). This resulted in an overall microfilarial prevalence (all ages) of 70%, representing an hyperendemic area (a microfilarial prevalence above 60% – see Table 1.1). (The parameterisation of the relationship between microfilarial prevalence and microfilarial load is described in section 2.8.4.) Understanding the long-term impact of ivermectin in hyperendemic areas is particularly important, as they will be the ones in which controlling the disease has the highest priority (morbidity will be more severe), elimination of the infection reservoir is likely to be more difficult and take longer (Winnen *et al.* 2002), and from which the infection could reinvade controlled areas.

2.3.2. Ivermectin effects

The model has previously been modified to incorporate the temporal dynamics of the microfilaricidal and embryostatic effects of a single ivermectin treatment (Basáñez *et al.* 2008; Churcher & Basáñez, 2008). This was further extended to allow ivermectin to have a cumulative adverse effect on microfilarial production (i.e. anti-macrofilarial action), as in ONCHOSIM. (The equations modelling this effect are described in section 2.8.2).

After each dose of ivermectin there is a microfilaricidal effect with 99% efficacy, and a reduction in microfilarial production (embryostatic effect) by fertile female worms (Basáñez *et al.* 2008). The ivermectin-exposed adult worms were then assumed either to: a) reach a new microfilarial production rate which is reduced by 30% ten months after each treatment round (representing a cumulative effect, depicted in Figure 2.2A), or b) resume microfilarial production, which ten months after each treatment would reach 70% of its baseline value i.e. is also reduced by 30 % from baseline, but the reduction is not additive (representing a non-cumulative effect, as concluded in (Bottomley *et al.* 2008), and illustrated in Figure 2.2B).

For the sake of comparison, this chapter compared ivermectin having a strong cumulative impact on microfilarial production (i.e. a large anti-macrofilarial action), as assumed in ONCHOSIM (Winnen *et al.* 2002)) verses having no cumulative effect (Bottomley *et al.* 2008). However, other possible scenarios such as a smaller more gradual adverse effect on

adult worms (potentially due to possible effects on intranodular sex ratios or a reduction in the longevity adult worms – see section 1.6) was not considered. This is addressed in the next chapter.

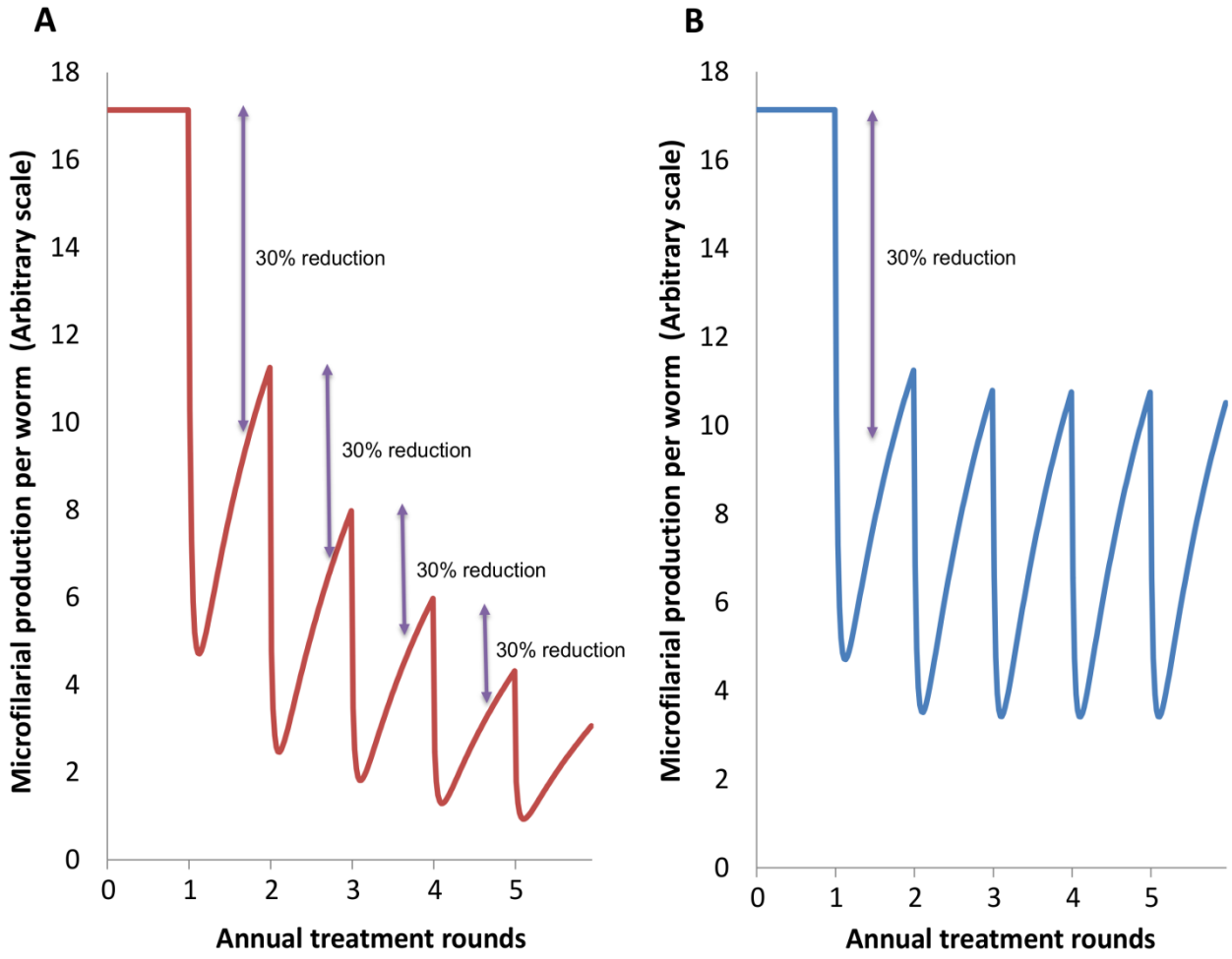

Figure 2.2. Schematic representation of two different proposed effects of ivermectin on *Onchocerca volvulus* microfilarial production. *The schematic represents a closed population of adult worms (i.e., no incoming worms due to transmission or worm death).* ***A:*** *Ivermectin is assumed to have a large cumulative effect on adult worm fertility by which the microfilarial production of ivermectin-exposed adult worms is reduced by 30% after each treatment round (red solid line).* ***B:*** *Ivermectin is assumed not to have a cumulative effect; ivermectin-exposed adult worms resume microfilarial production to 70% of its baseline value ten months after each treatment (Basáñez et al. 2008) (blue solid line).*

Although the cumulative reduction proposed in Plaisier *et al.* (1995) was estimated from data corresponding to annual ivermectin distribution (Alley *et al.* 1994), it was assumed that in the case of biannual treatments, each 6-monthly treatment causes the same proportional reduction. An analysis of the sensitivity of model outputs to this assumption was conducted following Winnen *et al.* (2002). Ivermectin was assumed to have intact efficacy, i.e. no sub-optimal response (Osei-Atweneboana *et al.* 2007).

2.3.3. Treatment coverage, compliance, and frequency

The model was further stratified into four treatment compliance classes (section 2.8.1): a first group who takes treatment every round; two groups who take treatment every other round alternately, and a fourth group who never takes treatment. The latter class represents individuals in the community who are systematic non-compliers, as opposed to a situation in which a proportion of individuals sometimes miss some treatment rounds (e.g. because they are absent or pregnant at the time of treatment). The proportion of systematic non-compliers was set at 0.1%, 2%, and 5% to investigate its effect on model outputs. These values were chosen to explore potential variability in this parameter. A recent ivermectin compliance study reported that 6% had never taken the drug over the course of eight consecutive treatment rounds (Brieger *et al.* 2011) (but the proportion of those never taking treatment may decrease over time). The four compliance groups were assumed not to differ in exposure to vectors (which depends on age and sex according to Filipe *et al.* (2005)). Children under five years were not treated in the model as they are not eligible to receive ivermectin.

2.3.4. Examined outputs and sensitivity analysis

The model was used to explore the effect of 15 years of (annual or biannual) mass ivermectin distribution on: a) microfilarial intensity (defined as mean (arithmetic) microfilarial load per mg of skin in those aged ≥20 years), and b) prevalence of microfilaridermia in the overall population. 15 years was chosen as a suitable timescale to investigate the impact of long-term of ivermectin, motivated by the epidemiological studies in Mali, Nigeria, and Senegal (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012).

The sensitivity of the above model outputs was explored with regards to the following assumptions: a) strong cumulative effect of ivermectin on microfilarial production (present vs. absent); b) overall therapeutic coverage (proportion of the total population receiving ivermectin at each round: 60%, 70%, 80%); c) proportion of systematic non-compliers (proportion of the eligible population who never take treatment): 0.1%, 2%, 5%); and d) treatment frequency (annual vs. biannual). In order to explore the extent to which the results were sensitive to the assumption that each biannual treatment caused the same proportional reduction on microfilarial production as an annual treatment (30% per dose), the analysis was repeated with a more conservative reduction of 16.5% per 6-monthly treatment (which gives an overall annual reduction of 30%).

2.4. Results

2.4.1. Cumulative vs. non-cumulative effect of ivermectin on microfilarial production

Model outputs indicate that the assumption of a strong cumulative impact of ivermectin on microfilarial production (i.e. a large anti-macrofilarial action) has a substantial effect on projections of long-term ivermectin treatment (Figure 2.3). Regarding microfilarial intensity (in adults aged 20 years and older), there would be a very pronounced decrease partly due to little repopulation of the skin by Mf, and partly due to the ensuing suppressed transmission. This is because, under this conjecture, the model assumes that the fertility of ivermectin-exposed adult worms would progressively be reduced to a very low level. By contrast, under the assumption of ivermectin not exerting a strong cumulative effect on microfilarial production, there is a substantial amount of repopulation of the skin by Mf in between annual treatments, leading to more transmission and a smaller overall impact on microfilarial intensity.

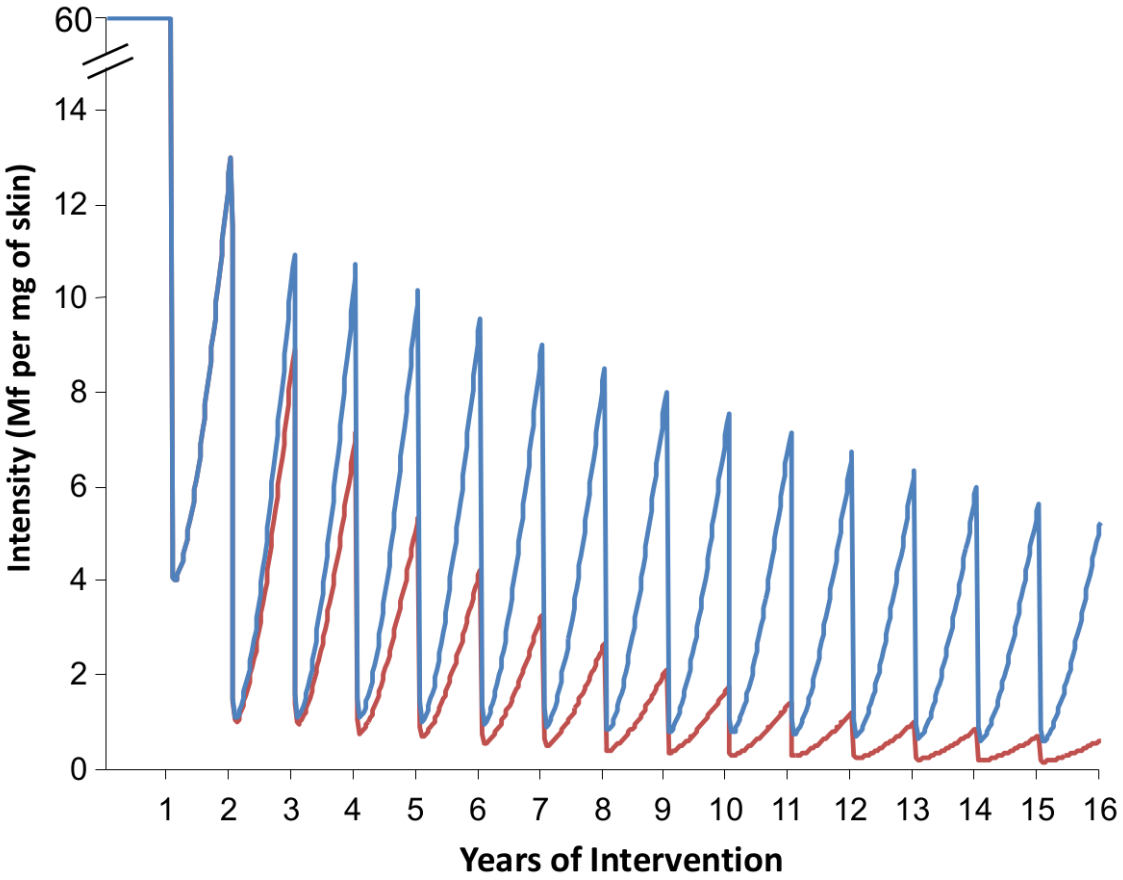

Figure 2.3. Impact on microfilarial intensity of annual ivermectin distribution under two assumptions of ivermectin effects. *The red and blue solid lines represent, respectively, model outputs assuming the operation of a strong cumulative impact on the fertility of O. volvulus (illustrated in Figure 2.2A), or the absence of such an effect (Figure. 2.2B). Results shown assume a pre-control microfilarial prevalence of 70% (all ages), a therapeutic coverage of 80%, and 0.1% of systematic non-compliance. Microfilarial intensity is quantified as the mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years.*

2.4.2. Annual vs. biannual treatment frequency

Assumptions regarding the operation or absence of a strong cumulative effect of ivermectin on microfilarial production can also influence the expected relative benefits of annual vs. biannual treatment frequency regarding reductions in microfilarial intensity, prevalence, and

transmission. In the presence of a cumulative reduction with each treatment round, there is initially a very marked benefit of the biannual distribution on the reduction of parasitological indicators (as the fertility rate is rapidly reduced). However, after repeated treatments, there would be much less difference in the long-term impact of ivermectin treatment on microfilarial prevalence compared to an annual treatment strategy (Figure 2.4A). In the absence of a cumulative effect, biannual treatments are more beneficial both in the short and long terms in reducing microfilarial prevalence than annual treatments (Figure 2.4B). With the more conservative 16.5% reduction in female fertility per 6-monthly treatment, the initial benefit of microfilarial prevalence reduction is less pronounced than in the previous scenario, but again, there is little difference in the long-term impact of biannual compared to annual ivermectin treatments (Figure 2.5).

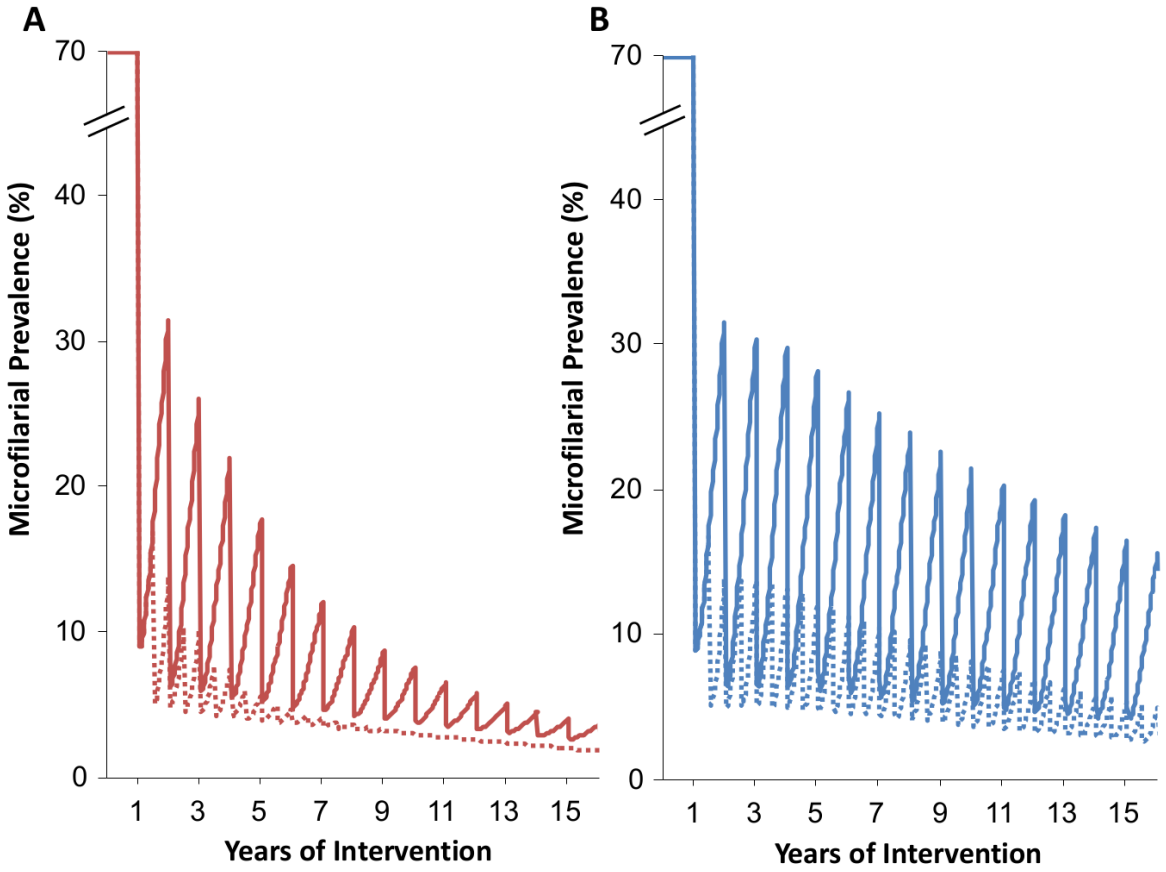

Figure 2.4. Impact on microfilarial prevalence of annual/biannual ivermectin distribution under two assumptions of ivermectin effects. *Solid and dashed lines represent, respectively, annual and biannual treatment frequency.* ***A:*** *Red lines correspond to model outputs assuming that ivermectin exerts a large cumulative reduction in microfilarial production by the adult female worm.* ***B****: Blue lines correspond to model outputs assuming the absence of such cumulative reduction. Assumptions are as in Figure 2.3.*

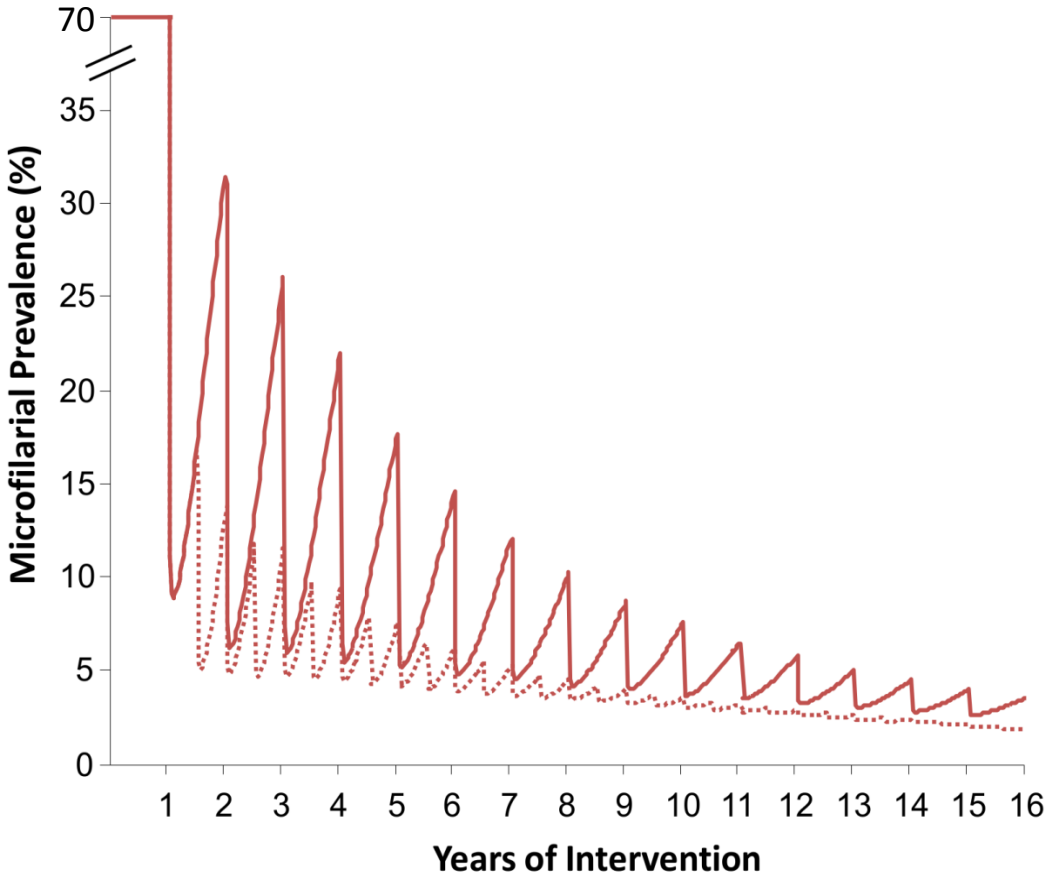

Figure 2.5. A comparison of the long-term impact of annual and biannual treatment strategies on microfilarial prevalence. *Solid and dashed lines denote, respectively, annual and biannual treatment frequency. Results assume that ivermectin exerts a large cumulative reduction in fertility, with a more pessimistic 16.5% reduction in the rate of microfilarial production per treatment when frequency is biannual. Assumptions are as in Figure 2.3.*

2.4.3. Therapeutic coverage and compliance patterns

Varying the therapeutic coverage in the overall population, and the proportion of systematic non-compliers had a large influence on the microfilarial intensity achieved at the end of the 15th year of ivermectin distribution. An increased overall coverage, or a decreased proportion of systematic non-compliers lead to lower microfilarial loads 12 months after the 15th year of intervention (Figure 2.6). Under annual treatment, overall coverage had a larger effect on projected microfilarial intensity (Figure 2.6A) and microfilarial prevalence (Figure 2.7A) than under biannual treatment (Figures 2.6B and 2.7B). (Because of the nonlinear relationship between microfilarial prevalence and intensity, the proportional reductions in prevalence are smaller.) For instance, under the assumption of a strong cumulative effect of ivermectin, and for a 5% proportion of non-compliers, increasing therapeutic coverage from 60% to 80% decreased microfilarial load by ~55% for annual frequency compared to 20% for biannual frequency. The corresponding values when no cumulative effect was assumed were ~34% and ~30%. By contrast, the assumed proportion of systematic non-compliers had a more pronounced effect on the impact of biannual treatment. Under the assumption of a strong cumulative effect of ivermectin, and for a 70% therapeutic coverage, decreasing systematic non-compliance from 5% to 0.1% decreased microfilarial load by ~54% for annual frequency and by ~97% for biannual frequency. The corresponding values when no cumulative effect was assumed were ~20% and ~53%.

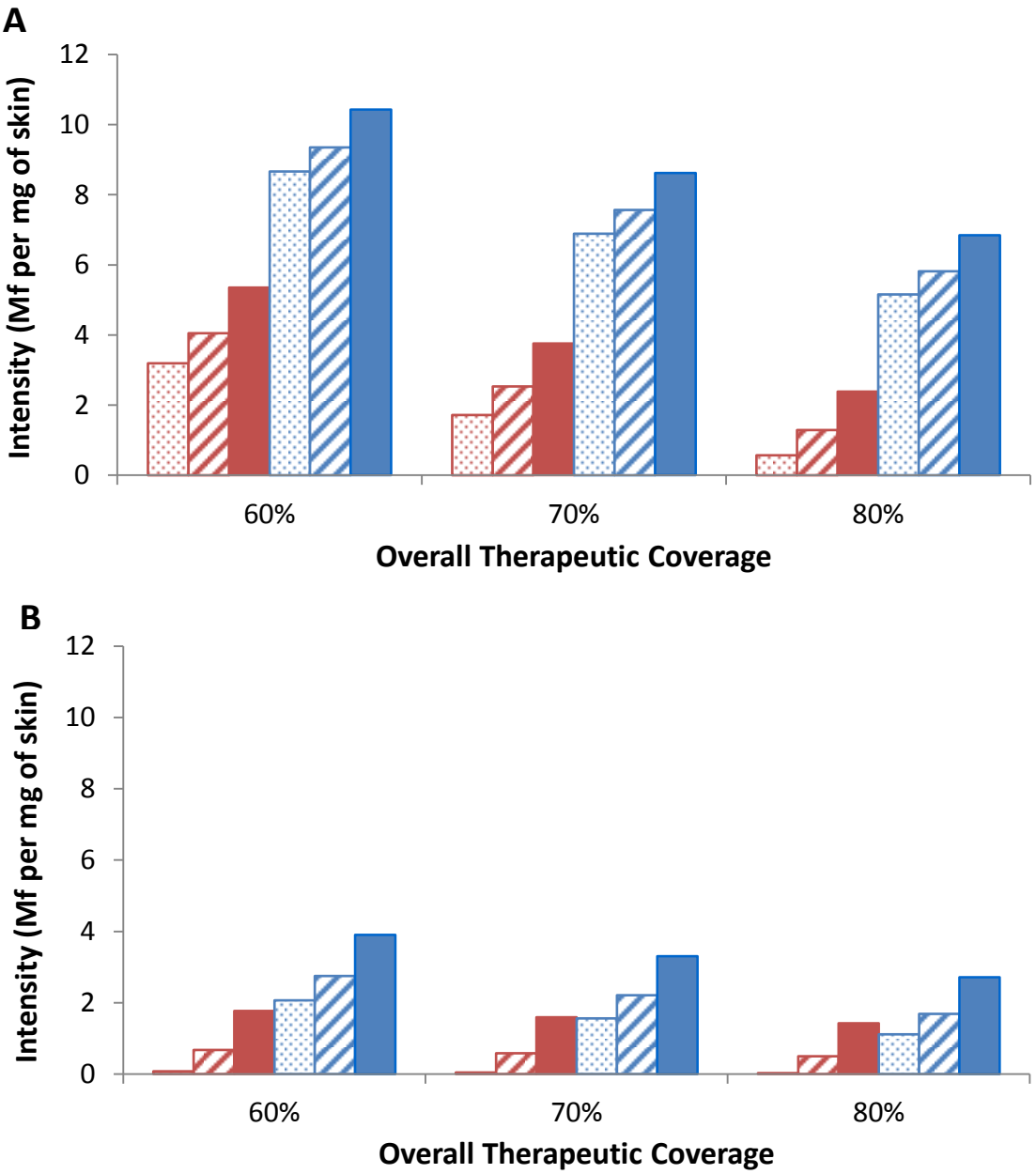

Figure 2.6. The effect of coverage and compliance on microfilarial intensity after 15 years of ivermectin treatment. *Panels **A** and **B** correspond respectively, to one year after the 15th treatment (for annual frequency), and one year after the 30th treatment (for biannual frequency). Red and blue bars represent, respectively, a cumulative and a non-cumulative effect of ivermectin on microfilarial production by the female worm. Dotted bars: 0.1% systematic non-compliance; dashed bars: 2% systematic non-compliance; solid bars: 5% systematic non-compliance. Assumptions are as in Figure 2.3. Microfilarial intensity is quantified as the mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years.*

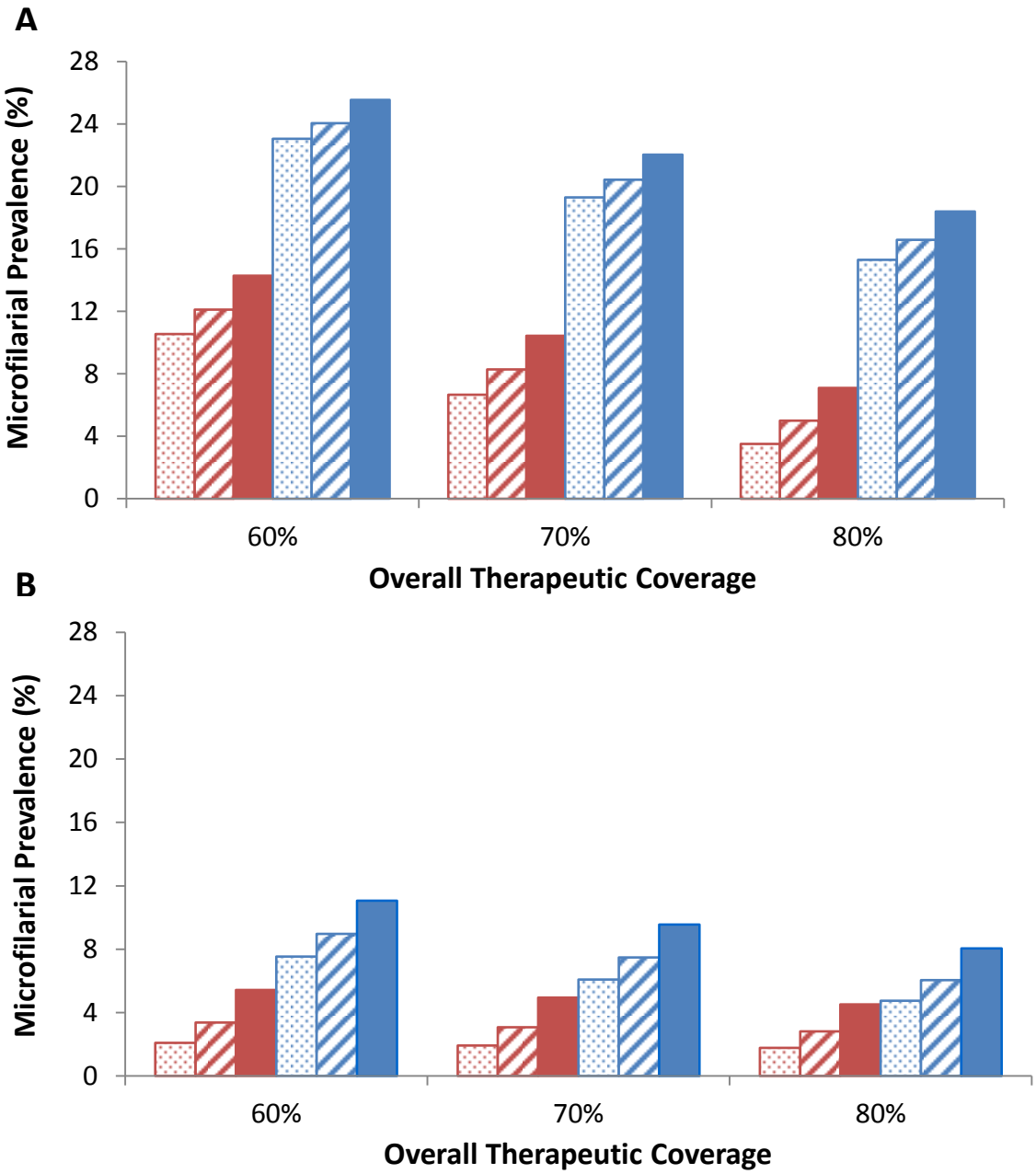

Figure 2.7. The effect of coverage and compliance on microfilarial prevalence after 15 years of ivermectin treatment. *Panels **A** and **B** correspond respectively, to one year after the 15th treatment (for annual frequency), and one year after the 30th treatment (for biannual frequency). Red and blue bars represent, respectively, a cumulative and a non-cumulative effect of ivermectin on microfilarial production by the female worm. Dotted bars: 0.1% systematic non-compliance; dashed bars: 2% systematic non-compliance; solid bars: 5% systematic non-compliance. Assumptions are as in Figure 2.3.*

2.5. Discussion

2.5.1. Cumulative vs. non-cumulative effect of ivermectin on microfilarial production

Mathematical models can play a fundamental role in informing control programmes, but crucially, policy makers must realise that model outputs are highly dependent on implicit and explicit model assumptions (Basáñez *et al.* 2012). Among the latter, is the effect long term ivermectin has on *O.volvulus* adult worms, which represents an area of considerable uncertainty where further research is urgently needed. These results illustrate that the question of whether or not ivermectin effects on female microfilarial production are strongly cumulative i.e. ivermectin has a large anti-macrofilarial action, is highly influential on the projections of the long-term effect of annual or biannual MDA with ivermectin, particularly in areas with high baseline onchocerciasis endemicity. An appropriate and updated incorporation of any action on adult worms into models, will be essential to reliably inform control policy, and fully assess ivermectin efficacy (Chavasse *et al.* 1993; Cupp *et al.* 2004; Cupp *et al.* 2011; Duke, 2005; Duke *et al.* 1990; Duke *et al.* 1991b; Gardon *et al.* 2002; Tekle *et al.* 2012; Whitworth *et al.* 1996a).

ONCHOSIM's projections indicate that with a high coverage of annual ivermectin distribution, elimination of onchocerciasis from most endemic foci in Africa is possible (Table 2.1). However, ONCHOSIM's simulations assume that ivermectin has a strong cumulative effect on microfilarial production (i.e. a large anti-macrofilarial action), and the results presented in this chapter suggest that, in the absence of such an effect, ivermectin would have a less pronounced long-term impact in areas with a high pre-control endemicity. This indicates that if ivermectin does not have a large anti-macrofilarial action, a longer duration of ivermectin distribution than previously estimated may be required, especially in areas with a high initial infection intensity and perennial transmission.

These results are compatible with those of other modelling studies (Duerr *et al.* 2011), which indicate that the higher the transmission intensity, the higher the necessary effectiveness of treatment (a net measure comprising coverage, number of treatment rounds per year and drug efficacy) to reach elimination. However, the results of this chapter also emphasizes how

different modelling assumptions can have profound effects on model outcomes and conclusions (a more extensive summary of the main structural assumptions of different onchocerciasis models is presented in Basáñez & Ricardez-Esquinca (2001)). This further highlights the need, discussed in Basáñez *et al.* (2012) for helminth modellers to investigate key questions regarding helminth control more collaboratively, exploring the reasons for any disparity between the results of different models using the best available data.

2.5.2. Annual vs. biannual treatment frequency

Biannual ivermectin treatment was found to have a large additional benefit in both reducing microfilarial prevalence and intensity compared to annual treatment when no cumulative reduction on microfilarial production was assumed. When such a cumulative effect was assumed, the model indicated that there would be an initial substantial benefit (as worm fertility is reduced quickly) of the biannual strategy, but that there would be relatively little difference in Mf prevalence at the end of the 15th year compared to annual treatment (Figure 2.4A). A possible reason for the pronounced difference between the two treatment frequencies, if ivermectin does not decrease worm fertility cumulatively, is that there would be substantially more transmission between annual than between 6-monthly treatments (distributing the drug every 6 months does not allow the adult worms to regain their fertility to a substantial level). Understanding ivermectin's effect on the reproduction and survival of adult worms has important policy implications regarding switching to a biannual (or more frequent) treatment strategy in Africa.

2.5.3. Therapeutic coverage

Varying therapeutic coverage (for fixed non-compliance) had less effect on the impact achieved with a biannual treatment frequency than it had for annual distribution. This can be explained as the model accounts for the fact that if someone misses a treatment round, there is another chance to get treated during that year, ensuring that at least one annual treatment is received. With an annual frequency, a missed treatment would result in a gap of at least two years between treatments, allowing microfilaridermia levels to build-up and contribute to transmission in the between-treatments period. This has implications regarding policy decisions in areas that have been found to have low coverage in the past, and highlights the potential benefit of switching to a biannual treatment strategy.

2.5.4. Compliance patterns

Assumptions regarding the proportion of systematic non-compliers were found to be just as influential as those for overall coverage when projecting the long-term impact of ivermectin distribution. The proportion of systematic non-compliance (for a fixed level of therapeutic coverage) was also found to have a marked influence on the impact achieved by a biannual treatment strategy, particularly when assuming a strong cumulative effect of ivermectin; the higher the non-compliance, the smaller the benefit of biannual treatment. This indicates that the effect of systematic non-compliance may not simply be overcome by increasing treatment frequency and has implications when considering switching to a biannual treatment strategy, as two areas with the same overall coverage but different proportion of systematic non-compliers may lead to very different results regarding the feasibility of elimination (Boyd *et al.* 2010).

As control programmes move towards elimination goals, the proportion of systematic non-compliers in the population becomes increasingly important. Studies of coverage and compliance for lymphatic filariasis treatment have indicated that, in addition to heterogeneity in transmission and vector density, and missed rounds of MDA, continuing transmission seems to be linked to rates of systematic non-compliance (Boyd *et al.* 2010). Therefore, when evaluating the progress of elimination programmes, the proportion of, and factors contributing to, systematic non-compliance should be investigated in addition to those determining overall coverage (Brieger *et al.* 2012; Brieger *et al.* 2011), as an assessment of the latter on its own may mask reasons behind transmission persistence.

Modelling studies should also routinely vary the proportion of systematic non-compliers in addition to levels of treatment coverage as part of their sensitivity analysis to help understand the impact of prolonged treatment in populations. Although there are some data indicating that treatment compliance may depend on host age and sex, Brieger *et al*. (2012) found that older members of the community were more likely to take ivermectin than younger sections of the population, and men were more likely to comply than women in a Cameroon, Nigeria and Uganda multi-centre study. Further investigation regarding patterns of systematic non-compliance (i.e. the characteristics of individuals who never take the drug) will be essential to parameterise such modelling studies.

2.6. Conclusions

There is substantially more uncertainty surrounding model-derived projections of the long-term impact of and the feasibility of onchocerciasis elimination with ivermectin distribution than previously recognised. When assuming that ivermectin does not have a strong cumulative effect on microfilarial production (Bottomley *et al.* 2008; Pion *et al.* 2013), i.e. not a large anti-macrofilarial action, these results indicate that it may not be feasible to eliminate onchocerciasis in areas with high pre-control endemicity with annual ivermectin alone. This highlights the need for the further consideration and economic evaluations of alternative treatment strategies, such as biannual treatment. Furthermore, these projections indicate that the proportion of systematic non-compliers in the population will be a key determinant of the success of the control programmes and emphasises the need for this to be recognised when evaluating the progress of the programmes and included in modelling studies.

2.7. Limitations

EpiOncho is a deterministic model and does not account for the influence of random events. Therefore it cannot be used to formally investigate the probability of reaching elimination, which requires a more complicated stochastic model.

The model's parameters for vector competence, survival, and host choice were those for savannah species of the *S. damnosum* s.l. complex (*S. damnosum* s. str and *S. sirbanum*) (Basáñez *et al.* 2009; Filipe *et al.* 2005). The influences of the potential uncertainties surrounding the key biological parameters (such as the combinations of vectors and life-expectancy of the adult worms) on the impact of control require further investigation. Furthermore the host population structure is only parameterized for one area (Filipe *et al.* 2005).

Moreover, the presented results assume that transmission is perennial i.e. occurs all year. Further investigation of the influence that different seasonal patterns of transmission and the relative timing of drug distribution have on the overall impact of long term is needed.

2.8. Supporting Information for Chapter 2

2.8.1. Onchocerciasis population dynamics model

The system of partial differential equations is based on a host age- and sex-structured onchocerciasis dynamics model presented by Filipe *et al.* (2005), and modified to incorporate the effects of repeated ivermectin treatment and treatment compliance. These equations describe, respectively, the rate of change with respect to time and host age of the numbers of non-fertile, N, and fertile, F, adult female worms per host, of Mf per milligram of skin, M, and of infective (L3) larvae, L, per blackfly vector. The host population (and subsequently the parasite population) is partitioned into different treatment groups according to how regularly they receive ivermectin treatment (a group who takes treatment every round; two groups who take treatment every other round alternately, and a fourth group of systematic non-compliers who never takes treatment). These different compliance groups (are denoted with subscript d (their proportion in the population by η), host sex groups (males and females) with subscript s (their proportion in the population by q), τ is time since last treatment, and a is host age. Definitions and values of model parameters (for savanna *O. volvulus–S. damnosum* s. str. and *S. sirbanum* in northern Cameroon (Filipe *et al.* 2005)) are given in Table 2.2. Equations (omitting time and age dependencies on the left terms for simplicity, and assuming a balanced worm sex ratio) are as follows,

$$\frac{\partial N_{s,d}}{\partial t}+\frac{\partial N_{s,d}}{\partial a}=\frac{1}{2}m\beta\Omega_s(a-p)\delta_H[L(t-p)]L(t-p)\exp(-\mu_H p)+[\lambda_0+\lambda_1(\tau)]F_{s,d}(t,a)-(\varpi+\sigma_W)N_{s,d}(t,a) \quad (2.1)$$

$$\frac{\partial F_{s,d}}{\partial t}+\frac{\partial F_{s,d}}{\partial a}=\varpi N_{s,d}(t,a)-[\lambda_0+\lambda_1(\tau)+\sigma_W]F_{s,d}(t,a) \quad (2.2)$$

$$\frac{\partial M_{s,d}}{\partial t}+\frac{\partial M_{s,d}}{\partial a}=\phi[W_{s,d}(t,a),k_W]\varepsilon_d\psi_d(t)F_{s,d}(t,a)-[\sigma_{M_0}+\sigma_{M_1}(\tau)]M_{s,d}(t,a) \quad (2.3)$$

$$\frac{\partial L_{s,d}}{\partial t}+\frac{\partial L_{s,d}}{\partial a}=\beta\Omega_s(a)\delta_{V_0}M_{s,d}(t,a)-\sigma_L[M_{s,d}(t,a)]L_{s,d}(t,a) \quad (2.4)$$

$$L(t)=\sum_s\sum_d q_s\eta_d\int_a\rho(a)\Omega_s(a)L_{s,d}(t,a)\,da \quad (2.5)$$

Microfilarial intensity:
In the main text, microfilarial intensity refers to the mean (arithmetic) microfilarial load in those aged ≥20 years. This is calculated from Equation (2.3) by integrating over age (from a = 20 to $a = a_m$) and summing over sex s and compliance group d,

$$M(t)_{\geq 20} = \sum_s \sum_d q_s \eta_d \int_{a=20}^{a=a_m} \rho'(a) M_{s,d}(t,a)\, da\,, \tag{2.6}$$

where $\rho'(a)$ is the probability density function of host age between 20 and a_m = 80 years,

$$\rho'(a) = \frac{\mu_H \exp(-\mu_H a)}{[\exp(-\mu_H 20) - \exp(\mu_H a_m)]}\,, \tag{2.7}$$

and μ_H is the per capita death rate of humans.

2.8.2. Modelling the cumulative effect of ivermectin

At any time after the start of a simulated treatment programme, the worm population in compliance group d comprises worms previously exposed to different numbers of ivermectin treatments. This is because: a) worms continually infect hosts throughout the treatment programme, and b) hosts in different compliance groups receive different numbers of treatments at different times. If ivermectin is assumed to suppress cumulatively the fertility of female *O. volvulus*, then the average reduction in fertility of the worm population will critically depend on the fraction of worms exposed to different numbers of treatments. To this end, n was defined as the maximum number of previous exposures to ivermectin, and n + 1 sub-models were formulated to track worm populations acquired during discrete time intervals throughout the course of a simulated treatment programme. Note that n varies among compliance groups (for example, for systematic non-compliers n = 0), and that some worms, acquired after the final treatment, will be unexposed to ivermectin (j = 0). The possibility of unexposed worms gives rise to the n + 1 (as opposed to n) sub-models.

Consider a treatment programme starting at time τ' (that is, the first dose of ivermectin is administered at time $t = \tau$'). Worms exposed to all n treatments ($j = n$) are acquired at time $t < \tau$'. By redefining the rate of establishment of female adult worms from Equation (2.1) as,

$$\Lambda_s(t,a) = \frac{1}{2} m \beta \Omega_s(a-p) \delta_H[L(t-p)] L(t-p) \exp(-\mu_H p), \tag{2.8}$$

the rate of establishment of adult worms exposed to all n treatments in compliance group d can be expressed as,

$$\Lambda_{s,d,j=n}(t,a) = \begin{cases} \Lambda_s(t,a) & \text{for} \quad 0 < t < \tau' \\ 0 & \text{otherwise.} \end{cases} \tag{2.9}$$

By contrast, unexposed worms (j = 0) are acquired after the last treatment which, if the n treatments were administered at frequency f, indicates that infection occurred at $t > \tau' + (n - 1)/f$. That is,

$$\Lambda_{s,d,j=0}(t,a) = \begin{cases} \Lambda_s(t,a) & \text{for} \quad \tau'+(n-1)/f < t < \infty \\ 0 & \text{otherwise.} \end{cases}. \tag{2.10}$$

It follows that the rate of establishment of adult worms exposed to the intervening numbers of ivermectin treatments j = 1, 2,…, n – 1 is given by,

$$\Lambda_{s,d,j=0}(t,a) = \begin{cases} \Lambda_s(t,a) & \text{for} \quad \tau'+(n-1-j)/f < t < \tau'+(n-j)/f \\ 0 & \text{otherwise.} \end{cases} \tag{2.11}$$

These conditions are used to define partial differential equations for the mean (arithmetic) number of female adult worms, $W_{s,d,j}(t,a)$, in each exposure group j = 0, 1,…, n,

$$\frac{\partial W_{s,d,j}(t,a)}{\partial t} + \frac{\partial W_{s,d,j}(t,a)}{\partial a} = \Lambda_{s,d,j}(t,a) - \sigma_W W_{s,d,j}(t,a). \tag{2.12}$$

Note that for the purposes of tracking adult worms exposed to different numbers of treatments, the fertility status (fertile/non-fertile) of female worms is not distinguished. Taking the expectation of $W_{s,d,j}(t,a)$ with respect to host age a and sex s yields,

$$W_{d,j}(t) = \sum_s q_s \int_a \rho(a) W_{s,d,j}(t,a)\, da\ , \tag{2.13}$$

where $\rho(a)$, the probability density function of host age, a, is

$$\rho(a) = \frac{\mu_H \exp(-\mu_H a)}{1 - \exp(-\mu_H a_m)}. \quad (2.14)$$

Summing over exposure groups gives the mean number of worms per host in compliance group *d*,

$$W_d(t) = \sum_{j=0}^{j=n} W_{d,j}(t). \quad (2.15)$$

The fraction of the total female worm population in ivermectin exposure group *j*, denoted $u_{d,j}(t)$, is now trivially given by,

$$u_{d,j}(t) = \frac{W_{d,j}(t)}{W_d(t)}. \quad (2.16)$$

Each subsequent exposure to ivermectin (after the first exposure) was assumed to cause a 30% reduction in female worm fertility (see main text), such that the fertility of female worms exposed to *j* treatments, Ψ_j, is given by,

$$\Psi_j = \begin{cases} 1 & \text{for} \quad j = 0 \\ (1-\zeta)^{j-1} & \text{for} \quad j > 0 \end{cases} \quad (2.17)$$

with parameter $\zeta = 0.3$ (Table 2.3). Note that for $j = 0$ (and for $j = 1$), $\Psi_j = 1$ indicates that worms previously unexposed to ivermectin, or exposed to a single dose ($j = 1$) have, respectively, full fertility, or the potential to regain full fertility (Basáñez *et al.* 2008). Subsequent treatments may cause a cumulative reduction of female worm fertility in this scenario.

The average reduction in female worm fertility in compliance group *d*, $\psi_d(t)$, is calculated using the fraction of the total worm population in each exposure group $u_{d,j}(t)$ (Equation (2.16)) and Ψ_j (Equation (2.17)),

$$\psi_d(t) = \sum_{j=0}^{j=n} \Psi_j u_{d,j}(t). \quad (2.18)$$

Definitions and values of parameters are given in Table 2.3.

2.8.3. Mating probability

It is assumed that the distribution of adult worms among hosts of the same compliance group is adequately described by a negative binomial distribution (NBD) with arithmetic mean (female) worm load, $W_{s,d}(t,a)$, and overdispersion parameter, k_W. Assuming polygamous mating (i.e., a single male can fertilise all females within a host) and a balanced worm sex ratio, the probability that a female worm is mated according to May, (1977) is,

$$\phi[W_{s,d}(t,a),k_W] = 1 - \left[1 + \frac{W_{s,d}(t,a)}{k_W}\right]^{-(k_W+1)}. \qquad (2.19)$$

Note that the degree of overdispersion of the adult worm population (inversely measured by the value of k_W) is assumed to be unaffected by ivermectin treatment. Definitions and values of parameters are given in Table 2.4.

2.8.4. Microfilarial prevalence

Overall (all ages) microfilarial prevalence is derived by using a relationship between prevalence and microfilarial load at the community level in Cameroon (Figure 2.8). This relationship, previously described in Basáñez & Boussinesq, (1999), was refitted assuming an average (arithmetic mean) skin snip sample weight of 1.7 mg as opposed to the 2.84 mg used previously and based on Prost & Prod'hon, (1978). This lower weight was estimated using the mean skin snip weight from samples collected by Collins *et al*. (1992), and is in agreement with other studies (Emukah *et al.* 2004). The prevalence–intensity relationship assumes that the load of microfilaridermia per person is distributed according to a negative binomial distribution with an overdispersion parameter k_M. The best fit was obtained when k_M was allowed to be a function of mean (arithmetic) microfilaridermia load using a hyperbolic as opposed to the power functional form used in previous fits (Basáñez & Boussinesq, 1999). Assuming that the degree of microfilarial overdispersion does not depend on compliance group, $\pi_d(t)$ is given by,

$$\pi_d(t) = 1 - \left\{1 + \frac{M_d(t)}{k_M[M_d(t)]}\right\}^{-k_M[M_d(t)]} \tag{2.20}$$

where $M_d(t)$ is given by,

$$M_d(t) = \sum_s q_s \int_a \rho(a) M_{s,d}(t,a)\, da\,, \tag{2.21}$$

and k_M is given by,

$$k_M\left[M_d(t)\right] = \frac{k_0\, M_d(t)}{1 + k_1\, M_d(t)}\,. \tag{2.22}$$

The overall population prevalence at time *t* was obtained by summing $\pi_d(t)$ across compliance groups,

$$\pi(t) = \sum_d \eta_d\, \pi_d(t)\,. \tag{2.23}$$

Definitions and values of parameters are given in Table 2.4.

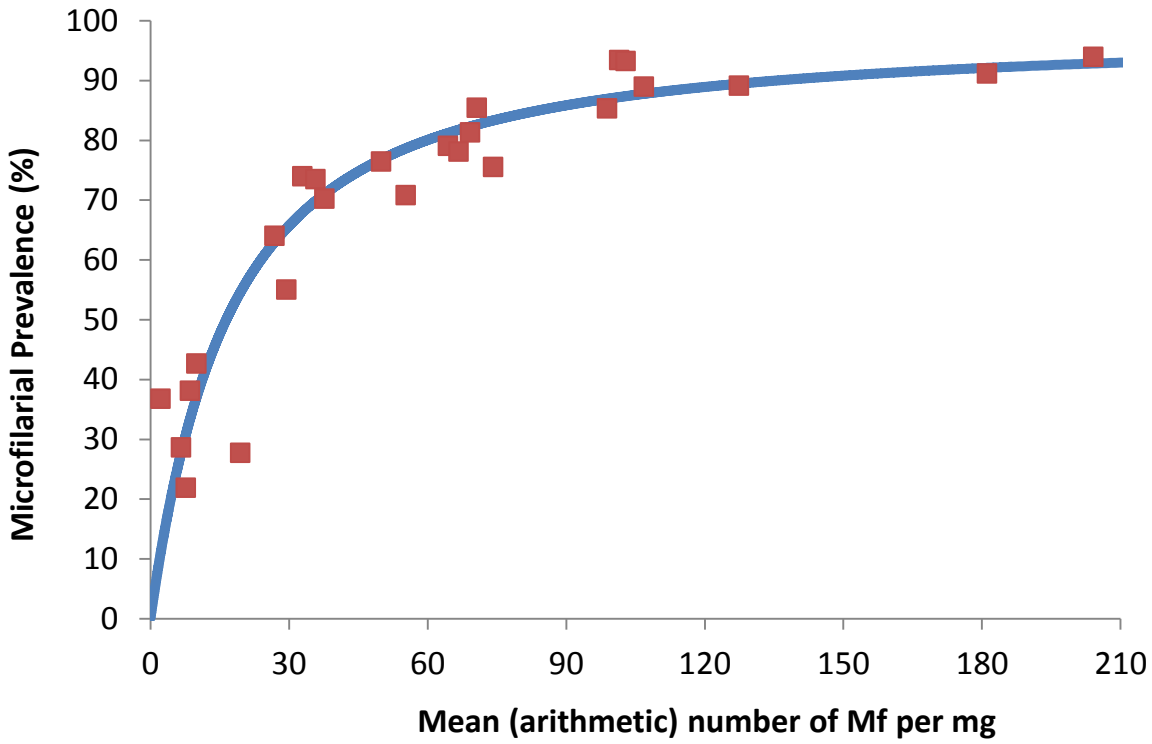

Figure 2.8. Observed and fitted microfilarial prevalence as a function of mean microfilarial load. *The data are from 25 north Cameroonian villages studied by Boussinesq, (1991) and presented in Basáñez & Boussinesq, (1999). It was assumed that on average there skin snip sample weighs 1.7 milligrams (as opposed to the 2.84mg quoted in Prost & Prod'hon, (1978)). Red markers correspond to the age- and sex-adjusted microfilarial prevalence in the communities (Basáñez & Boussinesq, 1999). The blue line is the function given in Equation (2.20) with maximum likelihood estimates* $k_0 = 0.013$ *and* $k_1 = 0.024$ *(Table 2.4).*

Table 2.2. Definition and values of parameters and variables for the onchocerciasis population dynamics model

Symbol	Definition of variables and parameters	Expression, average value and units
	Pertaining to human host	
$N_{s,d}(t,a)$	Mean (arithmetic) number of non-fertile female adult worms per person at time (*t*) and age (*a*); subscript *s* denotes host sex and *d* denotes treatment compliance category	Equation (2.1)
$F_{s,d}(t,a)$	Mean (arithmetic) number of fertile female adult worms per person at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (2.2)
$M_{s,d}(t,a)$	Mean (arithmetic) number of microfilariae per milligram of skin at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (2.3)
$\delta_H[L(t)]$	Proportion of L3 larvae developing to adult worms within the human host as a function of the number of infective larvae received per unit time (Filipe *et al.* 2005)	$\frac{\delta_{H_0} + \delta_{H\infty} c_H m\beta L(t)}{1 + c_H m\beta L(t)}$
δ_{H_0}	Proportion of L3 larvae developing to adult worms within the human host when $m\beta L(t) \to 0$ (Basáñez & Boussinesq, 1999)	0.0854
δ_{H_∞}	Proportion of L3 larvae developing to adult worms within the human host when $m\beta L(t) \to \infty$ (Basáñez *et al.* 2002)	0.00299
c_H	Severity of transmission intensity-dependent parasite establishment within the human host (Basáñez *et al.* 2002)	5.86 x 10^{-3} yr per L3 larva
μ_H	The net rate of population loss (due to death, emigration and other process) determining the age distribution of the population (Filipe *et al.* 2005)	0.04 yr^{-1}
σ_W	Per capita death rate of adult worms (Basáñez & Boussinesq, 1999)	0.1 yr^{-1}
σ_{M_0}	Per capita death rate of microfilariae in the absence of ivermectin (Basáñez & Boussinesq, 1999)	0.8 yr^{-1}
ϖ	Per capita rate at which untreated, non-reproducing female worms become fertile (Basáñez *et al.* 2008)	0.59 yr^{-1}
λ_0	Per capita rate at which untreated fertile female worms become non-fertile in the absence of ivermectin (Basáñez *et al.* 2008)	0.33 yr^{-1}
ε_d	Rate of production of microfilariae per fertile female worm scaled by the total weight (in milligrams) of microfilariae-bearing skin (Basáñez & Boussinesq, 1999; Duke, 1993)	1.1538 yr^{-1}
a_m	Maximum recorded human age in the reference population of northern Cameroon (Filipe *et al.* 2005)	80 yr
p	Prepatent period from infection with L3 larvae to presence of detectable microfilariae in the skin (Filipe *et al.* 2005)	2 yr

Table 2.2. Continued

Symbol	Definition of variables and parameters	Expression, average value and units
	Pertaining to human host (continued)	
$\rho(a)$	Probability density function of host age *a* (using a truncated exponential distribution of survival times) (Filipe *et al.* 2005)	$\frac{\mu_H \exp(-\mu_H a)}{1-\exp(-\mu_H a_m)}$
η_d	Proportion of the host population in compliance group *d*	–
q_s	Proportion of the host population in sex group (females/males) *s* (Filipe *et al.* 2005)	0.45/0.55
	Pertaining to simuliid vector	
$L(t)$	Mean (arithmetic) number of infective larvae per fly at time (*t*)	Equation (2.5)
m	Vector to host ratio (for ABR = 37,300 bites person^{-1} yr^{-1})	1196
β	Biting rate per fly on humans assuming a human blood index = 0.3 (Basáñez *et al.* 2002; Filipe *et al.* 2005)	31.2 yr^{-1}
δ_{V_0}	Proportion of ingested microfilariae developing to the infective stage within the vector, per bite (Filipe *et al.* 2005)	0.005
$\sigma_L[M_{s,d}(t,a)]$	Per capita net rate of loss of L3 larvae from vectors (Basáñez & Boussinesq, 1999)	$(a_H / g) + \sigma_{L_0} + \mu_V + \alpha_V M_{s,d}(t,a)$
a_H	Proportion of infective, L3 larvae shed per bite (Basáñez & Boussinesq, 1999)	0.5
g	Average duration between consecutive blood-meals (Basáñez & Boussinesq, 1999)	0.0096 yr
σ_{L_0}	Per capita death rate of L3 larvae within the vector (Basáñez & Boussinesq, 1999; Basáñez *et al.* 2002)	104 yr^{-1}
μ_V	Per capita death rate of uninfected blackflies (Basáñez & Boussinesq, 1999; Basáñez *et al.* 2002)	52 yr^{-1}
α_V	Parasite induced death rate of infected blackflies (Filipe *et al.* 2005)	0.6 yr^{-1} per microfilaria
$\Omega_s(a)$	Age- and sex-specific measure of exposure to vectors (Filipe *et al.* 2005)	$\begin{cases} E_s \gamma_s E_0, & a < a' \\ E_s \gamma_s \exp[-\alpha_s (a - a')], & a > a' \end{cases}$
E_s	Sex-specific exposure to vector bites (females/males) (Filipe *et al.* 2005)	0.90/1.08
E_0	Fraction of exposure at age 0 in relation to that at age *a*' from which exposure is allowed to change with age (Filipe *et al.* 2005)	0.10
γ_s	Normalisation factors to ensure that the distribution of bites among age groups sums to 1 (females/males) (Filipe *et al.* 2005)	0.548/1.154
α_s	Age-specific change in contact rate with vectors for human hosts of sex *s* (females/males) (Filipe *et al.* 2005)	–0.023/0.007

Table 2.3. Definition and values of parameters and variables for ivermectin treatment effects

Symbol	Definition of variables and parameters	Expression, average value and units
n	Maximum number of previous exposures to ivermectin by worms in a given compliance group	0 for those hosts never taking treatment to 15 (annual) or 30 (biannual) for those taking all treatments
f	Frequency of treatment	Annual or biannual
τ	Time since last ivermectin treatment	years
$\lambda_1(\tau)$	Excess per capita rate at which fertile females become non-fertile following ivermectin treatment (embryostatic effect) (Basáñez *et al.* 2008)	$32.4\exp(-19.6\tau)$ yr^{-1}
$\sigma_{M_1}(\tau)$	Excess per capita death rate of microfilariae following ivermectin treatment (microfilaricidal effect) (Basáñez *et al.* 2008)	$\left(\tau + 9.6\times10^{-3}\right)^{-1.25}$ yr^{-1}
τ'	Treatment programme start time	–
$\Lambda_{s,d,j}(t,a)$	The rate of establishment of female adult worms at time *t* in hosts of age *a*, sex *s*, treatment compliance group *d* and exposure group (number of treatments to which worms have been exposed to) *j*	Equations (2.9) and (2.10)
$W_{s,d,j}(t,a)$	Mean (arithmetic) number of female adult worms at time (*t*) and age (*a*); *s* denotes sex, *d* denotes treatment compliance category and *j* ivermectin exposure group	Equation (2.12) and (2.13)
$u_{d,j}(t)$	The fraction of the total worm population in exposure group *j*	Equation (2.16)
Ψ_j	The net reduction in fertility of adult worms in exposure group *j*	Equation (2.17)
ζ	The per dose reduction in fertility caused by ivermectin when a cumulative effect is assumed (Plaisier *et al.* 1995)	0.30
$\psi_d(t)$	The average reduction in fertility in compliance group *d*	Equation (2.18)

Table 2.4. Definition and values of parameters for mating probability and microfilarial prevalence calculations

Symbol	Definition of variables and parameters	Expression, average value and units
$\varphi[W_{s,d}(t,a),k_W]$	Mating probability at time *t*, age *a*, sex *s* and treatment compliance group *d*	Equation (2.19)
$W_{s,d}(t,a)$	Mean (arithmetic) number of female adult worms per person at time (*t*) and age (*a*), *s* denotes sex and *d* denotes treatment compliance category	$N_{s,d}(t,a)+F_{s,d}(t,a)$
k_W	Inverse measure of degree of overdispersion in the distribution of worms among hosts (Bottomley *et al.* 2008)	0.35
$\pi_d(t)$	Microfilarial prevalence at time *t* in compliance group *d*	Equation (*2*.20)
$k_M[M_d(t)]$	Inverse measure of the degree of overdispersion in the distribution of skin microfilariae among hosts of compliance group *d*, as a function of the mean (arithmetic) microfilarial load	Equation (*2*.22)
k_0	Parameters of the relationship between k_M and skin microfilarial load	0 013
k_1		0.024

Chapter 3: Impact of Ivermectin on Onchocerciasis and its Disease Burden

3.1. Summary

In this chapter a mathematical model of the dynamics of onchocercal disease is presented, which links documented associations between *Onchocerca volvulus* infection and the prevalence and incidence of morbidity and mortality to model outputs from EpiOncho (an onchocerciasis transmission model described in the previous chapter). This was used to assess the impact of annual ivermectin distribution on onchocercal infection and associated disease burden according to different endemicity and programmatic scenarios. It was found that annual ivermectin treatment is highly effective at reducing the disease burden associated with onchocerciasis; however, its overall impact on microfilarial prevalence and intensity depends strongly on baseline endemicity, treatment coverage and compliance. This indicates that although the goals of eliminating the public health burden of onchocerciasis will be met where long-term ivermectin distribution is feasible, those of eliminating the infection reservoir will depend on epidemiological and programmatic variables, precluding a one-size-fits-all approach to onchocerciasis elimination in Africa.

A modified version of this chapter is currently under review: Turner, H.C., Walker, M., Churcher, T.S. and Basáñez, M-G. Modelling the impact of ivermectin on River Blindness and its burden of morbidity and mortality in African savannah: EpiOncho projections.

3.2. Introduction

Human onchocerciasis is responsible for a considerable burden of disease and is associated with visual impairment, blindness, disfiguring skin disease, and severe troublesome itching (Duke, 1990). This is a protracted and chronic process because continual exposure to many infective vector bites is needed for the building up of a substantial worm burden and ensuing microfilarial infection, and because adult female worms (which produce hundreds to thousands of microfilariae (Mf) daily) live, on average, for ten years (Plaisier *et al.* 1991). The adult stages (macrofilariae) reside in worm bundles located subcutaneously (palpable nodules) or deeply in the body, where they produce the Mf which migrate to the skin (microfilaridermia) and the eyes (Bradley *et al.* 2005). Immunological responses to filarial products (Hall & Pearlman, 1999), either of parasite origin or particularly of their endosymbiotic *Wolbachia* bacteria (Tamarozzi *et al.* 2011), lead to long-standing, non-resolving inflammation associated with chronic onchocerciasis pathology (Brattig, 2004). Skin pathology ranges from troublesome itching to (disfiguring) skin changes, including early-stage reactive lesions, and late-stage depigmentation (leopard skin) and atrophy (Murdoch *et al.* 1993). Moreover, individuals with high microfilaridermia suffer an increased risk of death (Little *et al.* 2004b; Walker *et al.* 2012), independent of that related to blindness (Kirkwood *et al.* 1983) i.e. sighted individuals are also subject to an excess risk of death.

In practice, the impact of annual mass drug administration (MDA) with ivermectin on the burden of infection and (but not necessarily in the same manner) the burden of disease, will vary according to epidemiological and programmatic factors. Mathematical models of infection and disease dynamics can be used to understand and quantify how these variables affect the projected impact of control programmes. These so-called 'disease models' couple output from an infection transmission dynamics model to the prevalence and/or incidence of disease sequelae, using statistical relationships deduced from epidemiological data and formalising current understanding of the relationship between infection and morbidity. Such models have been developed for trachoma (Gambhir *et al.* 2009), soil-transmitted helminthiases (Chan *et al.* 1994), schistosomiasis (Chan *et al.* 1996; Medley & Bundy, 1996), lymphatic filariasis (Chan *et al.* 1998), and onchocerciasis (Coffeng *et al.* 2013), and are essential tools for conducting cost-effectiveness analysis of control interventions against these neglected tropical diseases (NTDs).

Spurred by the documented success in the Mali, Nigeria, and Senegal foci (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012), there has recently been a shift in onchocerciasis control policy in Africa, with the aim changing from morbidity control to elimination of infection (section 1.9). For instance, the APOC has a new goal of elimination of onchocerciasis where possible by 2025 (World Bank, 2012), and the London Declaration on Neglected Tropical Diseases (LDNTD), joined the World Health Organization's (WHO) 2020 Roadmap on NTDs (London Declaration on Neglected Tropical Diseases, 2013) and set goals for elimination of onchocerciasis in selected countries of Africa by 2020 (World Health Organization, 2013). Rigorous evaluation of the feasibility of achieving these targets, and of the benefits already accrued necessitates of the contribution of dynamic models of onchocerciasis infection and disease.

To this end, in this chapter a mathematical model of the dynamics of onchocercal disease is developed by linking documented associations between infection and morbidity to output from EpiOncho (described in the previous chapter). Incorporated in the model is the direct association between the intensity of infection with *O. volvulus* Mf and excess human mortality which has been omitted elsewhere (Coffeng *et al.* 2013), and not included in the recent estimates of the global burden of onchocercal disease (Murray *et al.* 2012). The model is used to assess the long-term impact of annual MDA of ivermectin on onchocercal infection and associated disease burden in savannah areas of Africa, and explore how this impact may depend on different epidemiological and programmatic scenarios.

3.3. Method

3.3.1. Disease model

An onchocerciasis disease model was developed by linking output from EpiOncho (described in Chapter 2) to the prevalence and incidence of onchocerciasis-associated morbidity and mortality (Figure 3.1). In particular, the average (arithmetic mean) microfilarial load over time; the corresponding microfilarial prevalence, and the prevalence of adult female worms, were coupled to the incidence and prevalence of blindness; visual impairment; prevalence of troublesome itch and the incidence of excess mortality. A summary of how each disease state was represented is found below, with a further detailed description provided in section 3.8.

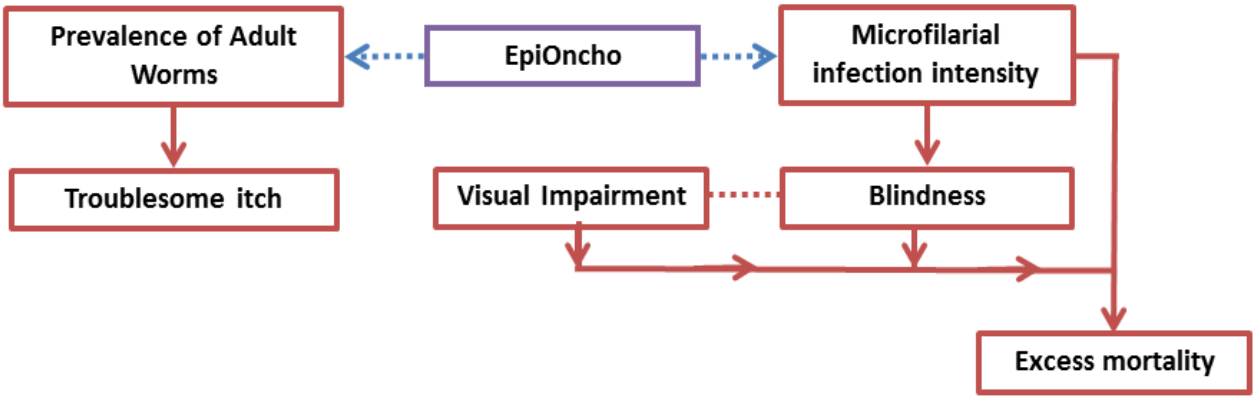

Figure 3.1. Schematic representation of the disease model. *The prevalence of troublesome itch was estimated based on a relationship with the prevalence of adult female worms, previously derived using the ONCHOSIM model (Coffeng et al. 2013; Habbema et al. 2007). The incidence of blindness was estimated as a function of microfilarial load (lagged by 2 years) based on a log-linear Poisson model (Little et al. 2004a). The number of individuals with visual impairment was estimated using a published ratio between the prevalence of visual impairment and that of blindness (Remme, 2004a). Excess mortality due to onchocerciasis was assumed to occur via mortality among individuals suffering onchocerciasis-related vision loss (blindness and visual impairment) (Kirkwood et al. 1983; Shibuya et al. 2006), plus an (independent from the former) risk of mortality among sighted individuals with high microfilarial load (lagged by 2 years) (Little et al. 2004b; Walker et al. 2012).*

Vision Loss:

The number of people blind due to onchocerciasis (defined as corrected visual acuity of <3/60 or restriction of visual field to less than 10° in the better eye (Remme, 2004a)), was calculated by means of a partial differential equation comprising two rates, namely, the incidence of new onchocercal related blindness cases, and the loss of already blind individuals due to (excess) mortality (Kirkwood *et al.* 1983; Shibuya *et al.* 2006). The former rate was estimated based on a log-linear Poisson model developed by Little *et al.* (2004a), which describes incidence of blindness as a function of microfilarial load lagged by 2 years (fitted to the cohort dataset of the Onchocerciasis Control Programme in West Africa (OCP)). The Poisson model assumes that the incidence of blindness is associated with lagged microfilarial load (a 2-year lag provided the best fit to the data (Little *et al.* 2004a), probably reflecting that the loss of visual acuity of an individual in the present is associated with the microfilarial load of that individual in the past). Consequently, the decline in prevalence of vision loss was lagged by two years after the start of ivermectin distribution. The latter mortality rate, was calculated by multiplying the age-specific background mortality rate

(described in section 3.8.6) by an excess relative risk of mortality (of 2.5) according to (Shibuya *et al.* 2006).

The number of individuals with visual impairment or low vision (defined as corrected visual acuity of <18/60 and ≥3/60 in the better eye (Remme, 2004a)) caused by onchocerciasis was estimated using a published ratio of visual impairment to blindness (of 1.78) according to (Remme, 2004a). Prevalent blindness and visual impairment cases were assumed to be irreversible conditions and not to respond to ivermectin treatment (Ejere *et al.* 2001), which does not reverse established ocular sequelae (such as sclerosing keratitis and optic nerve atrophy).

Troublesome Itch:

Troublesome itch has been found to be associated with the presence of infection (Murdoch *et al.* 2002) but not with microfilarial infection intensity (Ghalib *et al.* 1987; Kipp & Bamhuhiiga, 2002). Due to this, the estimated prevalence of troublesome itch is based on a relationship between the prevalence of troublesome itch and that of adult female worms, previously derived using ONCHOSIM (Coffeng *et al.* 2013; Habbema *et al.* 2007). Troublesome itch was related to the presence of female adult worms because the association between the presence of Mf and troublesome itch does not hold during ivermectin treatment; the reduction in prevalence of itch being smaller and more delayed than the drop in microfilarial prevalence and load (Brieger *et al.* 1998b; Coffeng *et al.* 2013; Habbema *et al.* 2007). In addition, the therapeutic effect of ivermectin on troublesome itch was parameterised based on the results of a multi-centre trial of ivermectin for the treatment of onchocercal skin disease and severe itching (Brieger *et al.* 1998b) as described in section 3.8.5. Consequently, there is an initial sharp decline in the prevalence of troublesome itch (as a result of ivermectin's therapeutic effect) followed by a more gradual decrease as the prevalence of adult worms declines. Since the model assumes a pre-patent period of two years (Filipe *et al.* 2005; Prost, 1980b), there is a delay between the former and the latter.

Excess Mortality:

Excess mortality due to onchocerciasis was assumed to occur via an additional risk of mortality among individuals suffering onchocercal related vision loss (Kirkwood *et al.* 1983; 2006), and an additional (but independent from the former) risk of mortality among (sighted)

individuals with high microfilarial loads (Little *et al.* 2004b; Walker *et al.* 2012). The former was modelled using a excess risk of mortality among the blind and those with visual impairment that is, respectively, 2.5 and 1.5 times higher than that for those fully sighted (Shibuya *et al.* 2006). The latter was modelled using a published non-linear, host age-dependent association between the relative risk of mortality of sighted individuals and their microfilarial load (lagged by two years) estimated from the OCP dataset as mentioned above (Walker *et al.* 2012).

Disability-Adjusted Life Years (DALYs):
Disability-Adjusted Life Years (DALYs) due to onchocerciasis at baseline were used to quantify the pre-control burden of disease combining into a single metric the burden of onchocercal disease resulting from blindness, visual impairment, troublesome itching (years lived with disability, YLD), and premature death (years of life lost, YLL). The DALYs were estimated using the disability weights provided by the Global Burden of Disease (2004) study (World Health Organization, 2004). The equivalent disability weights from the Global Burden of Disease (2010) study (Salomon *et al.* 2012) were not used, because (other than blindness) they are stratified by severity levels. For example, the skin disease disability weights were stratified into three "disfigurement levels", and visual impairment into "mild", "moderate", and "severe". Without more detailed definitions, it was not possible to relate such levels to the modelled disease sequelae.

The YLLs were discounted at a rate of 3% per year—in agreement with WHO guidelines (World Health Organization, 2003). Furthermore, based on the methodology presented in the Disease Control Priorities Project (Disease Control Priorities Project, 2006), I did not apply any age weighting to DALY estimates (whereby healthy life lived at younger and older ages is given a lower weight than that at productive adult ages). Further description of the DALY calculations is provided in section 3.8.7.

3.3.2. Ivermectin's anti-macrofilarial effect

Although the initial clinical trial studies that investigated the effects of a single standard dose (150 µg /kg) of ivermectin have shown no evidence of a macrofilaricidal effect (killing of adult worms) (Albiez *et al.* 1988; Schulz-Key *et al.* 1985), various studies have reported that multiple doses over several years may have a cumulative adverse effect on adult worm

reproductive fitness / longevity (Chavasse *et al.* 1993; Cupp *et al.* 2004; Cupp *et al.* 2011; Duke, 2005; Duke *et al.* 1991b; Plaisier *et al.* 1995; Tekle *et al.* 2012; Whitworth *et al.* 1996a). Though, (as discussed in the previously chapter) this effect may not be as high as previously assumed (Plaisier *et al.* 1995), ivermectin may be having a small, gradual adverse effect on adult worms (potentially due to effects on intranodular sex ratios – see section 1.6). To account for this potential anti-macrofilarial action of long-term ivermectin MDA, it was assumed that each dose causes a 7% cumulative reduction in the per capita rate of microfilarial production by adult worms. This value was approximated by matching the model output (via varying the per dose reduction) to data on microfilarial load after three years of three-monthly ivermectin treatments (over twelve treatments rounds) presented in Gardon *et al*. (2002) for Cameroon. These authors estimated the magnitude and statistical significance of the ivermectin effect on female worm fertility to be greater than upon worm mortality; therefore, the former was chosen to represent a cumulative, per dose, anti-macrofilarial action of the drug. Despite the higher treatment frequency examined (three-monthly), this dataset was chosen to assess the per dose anti-macrofilarial action of the ivermectin, due to the number of treatement rounds the participants were exposed to (over twelve treatment rounds) and because the Mf load is presented per mg and not per skin snip (allowing for accurate comparison to EpiOncho's output); there is a lack of well-characterized long-term (individual) longitudinal data (including previous treatment history), to more accurately estimate the potential anti-macrofilarial action of ivermectin. This estimated per dose reduction is consistent with the epidemiological evaluation in Cameroon by Pion *et al.* (2013) (whose results do not support the operation of a strong cumulative effect of repeated ivermectin treatments and more broadly by the modelling study by Bottomley *et al.* (2008), which indicated that ivermectin did not have a cumulative effect on microfilarial production after two and a half years of six-monthly treatments (a relatively small reduction would have a minor initial impact, and thus may not have been detectable / statistically significant in the short time frame).

However, due to the importance of this parameter (as discussed in the previous chapter) the strength of the anti-macrofilarial action of ivermectin was varied in the sensitivity analysis (based on the 30–35% irreversible reduction estimated by Plaisier *et al*. (1995)).

3.3.3. Model outputs and sensitivity analysis

The model was used to estimate the overall microfilarial prevalence (all ages) and intensity (defined as microfilarial load per mg of skin in those aged ≥20 years) and its associated morbidity and mortality over the course of 15 annual ivermectin treatment rounds. As in the previous chapter, 15 years was chosen as a suitable timescale to investigate the impact of long-term treatment of onchocerciasis motivated by the epidemiological studies in Mali, Nigeria, and Senegal (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012). The model's outputs were stratified by the pre-control microfilarial prevalence, representing a range of hypo-, meso-, hyper- and highly hyperendemic onchocerciasis foci (Table 1.1) by varying the annual biting rate (ABR) of the simuliid vectors (Table 3.1). In addition, the pre-control DALY disease burden associated with onchocerciasis in African savannah areas was estimated within the range of endemicity explored.

The sensitivity of model projections was explored with regards to the following assumptions a) overall therapeutic coverage (proportion of the total population receiving ivermectin at each round) of 60% and 80% coverage; b) proportion of systematic non-compliance (proportion of the eligible population who never take treatment) of 5% and 0.1%; c) anti-macrofilarial effect of ivermectin (the, per dose, cumulative reduction in microfilarial production by ivermectin-exposed female adult worms) of 7% (small) and 30% (large) (Plaisier *et al.* 1995).

Table 3.1. Summary of baseline (pre-control) modelled epidemiological scenarios

Pre-control endemicity	Microfilarial prevalence in all ages	Annual biting rate (ABR)[§]	Annual transmission potential (ATP)[¶]	Mean (arithmetic) microfilarial intensity in all ages (Mf/mg)	Mean (arithmetic) microfilarial intensity in those aged ≥ 20 years (Mf/mg)
Mesoendemic	40%	7,300	88	11.2	18.7
Hyperendemic	60%	15,470	373	23.9	40.0
Highly hyperendemic	80%	85,800	4,290	58.9	98.0

[§] Annual biting rate (ABR): the average number of *Simulium* bites to which a person is exposed during a whole year.[¶] Annual transmission potential (ATP): the average number of infective larvae (L3) of *O. volvulus* potentially received during a whole year by a person exposed to the annual biting rate; model assumes perennial transmission. Both the ABR and ATP are for a proportion of vector blood meals of human origin equal to 0.3 (Basáñez & Boussinesq, 1999).

3.4. Results

3.4.1. Impact of ivermectin on microfilarial prevalence and intensity

Long-term (15 years of consecutive) annual ivermectin distribution is projected to reduce progressively and markedly (by more than 90%) the intensity of microfilarial infection (measured in the population aged ≥20 years). However, due to the dynamic nature of ivermectin's action on the production of Mf by adult female worms, and under conditions of ongoing transmission, these parasite stages will reappear in the skin (and be transmitted to vectors) between consecutive annual treatments (Figure 3.2A). The degree of skin repopulation by Mf is strongly related to pre-control endemicity level (reflecting initial adult worm burden as well as vector density) and is substantially larger for (highly) hyperendemic areas. Impact on microfilarial prevalence (all ages) is less marked than that on microfilarial intensity (due to the nature of the non-linear relationship between these two variables).The magnitude of the impact also deceases with increasing levels of pre-control endemicity (Figure 3.2B).

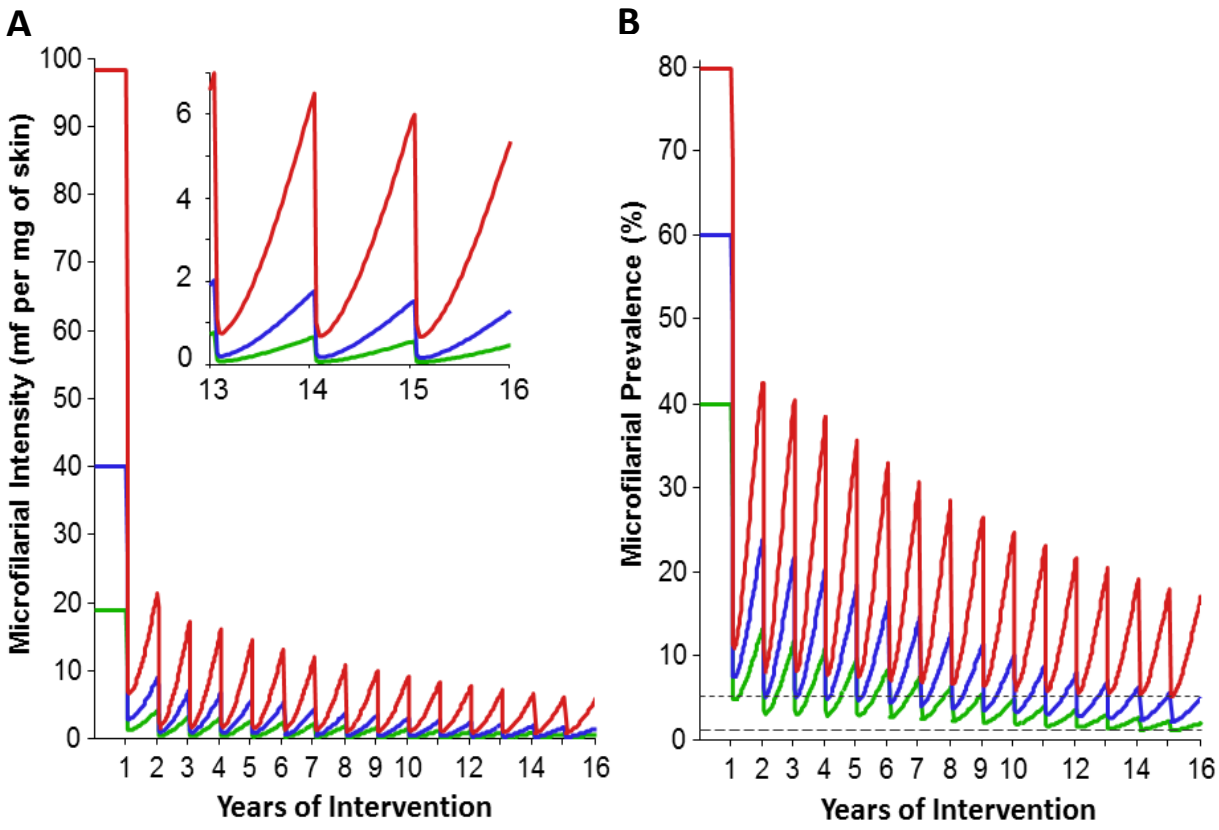

Figure 3.2. Impact of annual ivermectin distribution on the intensity (A) and prevalence (B) of microfilarial infection. *The red, blue and green lines correspond, respectively, to a baseline endemicity of 80%, 60% and 40% microfilarial prevalence. Intensity of infection is quantified as the mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years. The dashed horizontal lines illustrate the upper and lower bounds (5% and 1% prevalence) of the current operational thresholds for cessation of treatment, namely an observed a microfilarial prevalence below 5% in all surveyed villages and 1% in 90% of the surveyed villages) (African Programme for Onchocerciasis Control, 2010). Results shown assume a therapeutic coverage of 80%, 0.1% of systematic non-compliance, perennial transmission, and a 7% cumulative reduction in microfilarial production by female adult worms per ivermectin dose. The inset in Figure 3.2A zooms in microfilarial infection intensity (in the ≥20 yr of age) for the last four years of the simulated intervention programme.*

3.4.2. Pre-control disease burden

Before the inception of mass ivermectin distribution and in the absence of other control interventions, infection by *O. volvulus* in African savannah areas can be associated with a large burden of disease, which is non-linearly related to the baseline endemicity level. This is

illustrated by the pre-control (total) DALY burden stratified by level of baseline endemicity in Table 3.2 and Figure 3.3, which shows that relative to the burden for the mesoendemic level (represented by a microfilarial prevalence of 40%), the burden corresponding to the hyperendemic level is three times as high, and for the highly hyperendemic level (80% microfilarial prevalence at baseline), is seven times as high. At pre-control, onchocerciasis was found to be associated with high levels of blindness and visual impairment, with the baseline overall prevalence (across all ages) of onchocercal related blindness reaching over 8% in highly hyperendemic areas (Figures 3.4A and 3.4B). In addition, onchocerciasis was associated with high levels of troublesome itch (Figure 3.4C), with the estimated pre-control overall prevalence reaching over 30% in highly hyperendemic areas.

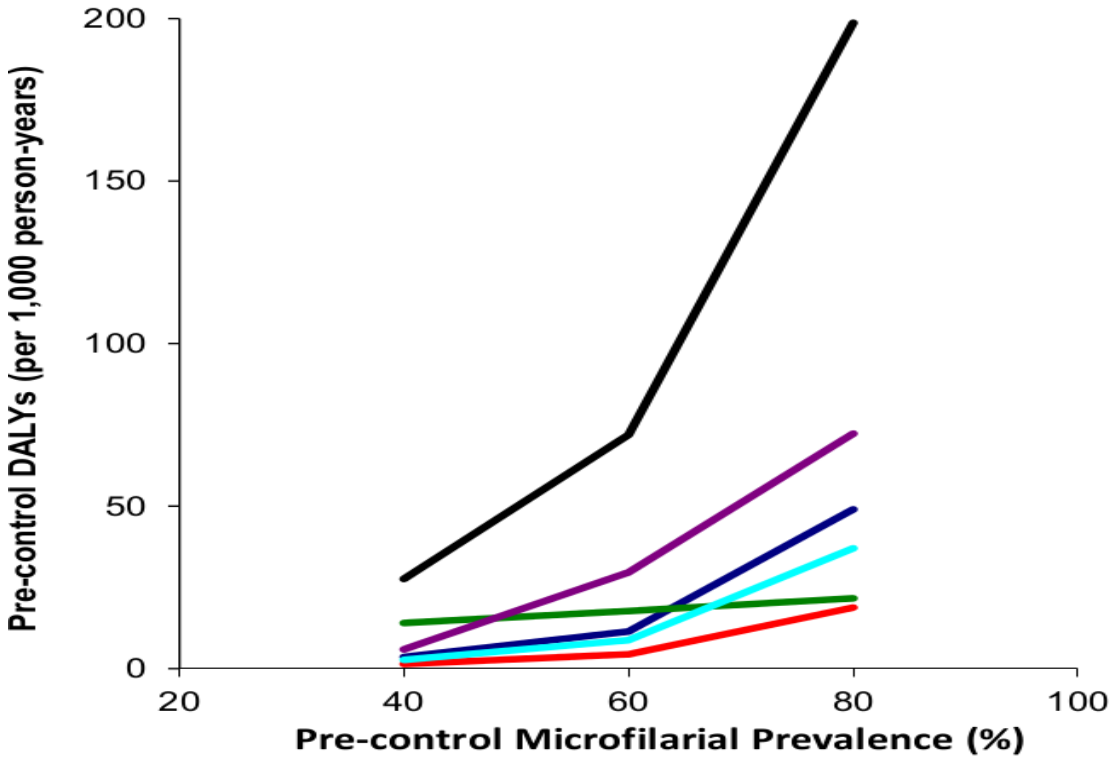

Figure 3.3. Relationship between the level of endemicity and pre-control disease burden associated with onchocerciasis in savannah areas of Africa. ■ *Total disability adjusted life-years (DALY) associated with onchocerciasis,* ■ *Years lived with disability (YLD) associated with onchocerciasis-related blindness,* ■ *YLD associated with onchocerciasis-related visual impairment,* ■ *YLD associated with onchocerciasis-related troublesome itch,* ■ *Years of life lost (YLL) associated with vision loss,* ■ *YLL associated with high microfilarial load.*

Table 3.2. Baseline (pre-control) model-derived burden of disease (DALYs) associated with onchocerciasis in savannah areas of Africa at different levels of endemicity

	Disability Adjusted Life Years[§] (per 1000 person-years)					
	Years lived with disability (YLD)			Years of life lost (YLL)[†]		
Pre-control endemicity	**Blindness**	**Visual impairment**	**Troublesome itch**	**Associated with vision loss**	**Associated with high microfilarial load**	**Total DALY burden [¶]**
Mesoendemic	3.6	1.4	14.0	2.7	5.9	27.6
Hyperendemic	11.4	4.4	17.7	8.8	29.6	71.9
Highly hyperendemic	49.0	18.8	21.6	37.0	72.3	198.7

[§] See section 3.8.7 for a detailed description of the methods used to calculate DALYs.[†] In line with WHO guidelines, a discount rate of 3% was applied to YLLs (World Health Organization, 2003). Pre-control microfilarial prevalence as in Table 3.1. [¶] In comparison, the 2010 global burden of disease project estimated that a total of 1040 DALY were lost (all causes) per 1000 people living in western sub-Saharan Africa in the year 1990 (Murray *et al.* 2012).

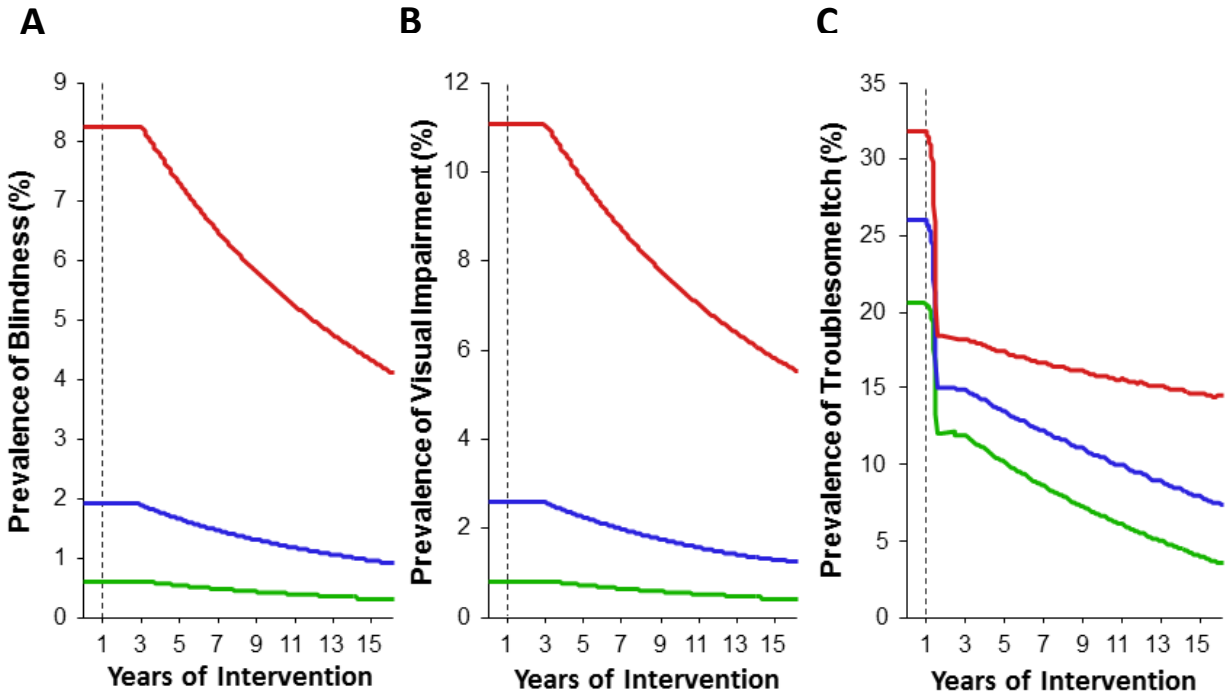

Figure 3.4. Impact of annual ivermectin distribution on the morbidity associated with onchocerciasis in the savannah areas of Africa. ***A:*** *Prevalence of blindness due to onchocerciasis (across all ages).* ***B:*** *Prevalence of visual impairment due to onchocerciasis (across all ages).* ***C:*** *Prevalence of troublesome itch due to onchocerciasis (across all ages). The red, blue and green lines correspond, respectively, to a baseline endemicity of 80%, 60% and 40% microfilarial prevalence. Assumptions are as in the legend of Figure 3.2. The commencement of the intervention at year 1 is represented by the vertical dashed lines. Delays in the decrease of blindness and visual impairment prevalence are due to a 2-year lag between vision loss in the present and microfilarial infection in the past. The initial sharp decline in the prevalence of troublesome itch is due to the assumed therapeutic effect of ivermectin followed by a more gradual decrease as adult worm prevalence declines.*

Onchocerciasis was also associated with a notable incidence of excess mortality, which increased non-linearly with the pre-control endemicity level (Table 3.2 and Figure 3.3). The YLLs associated with high microfilarial load were responsible for a substantially higher proportion of excess host mortality than those associated with onchocercal related vision loss (Table 3.2 and Figure 3.5).

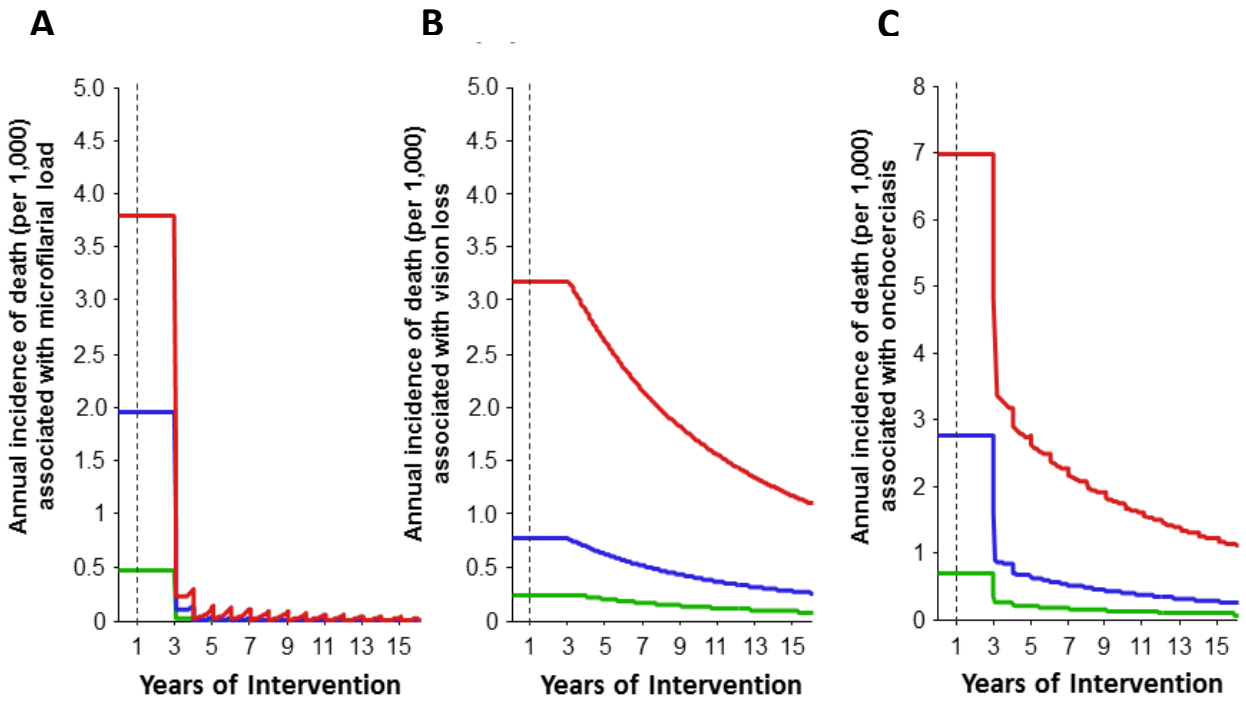

Figure 3.5. Impact of annual ivermectin distribution on the excess mortality associated with onchocerciasis in savannah areas of Africa. ***A:*** *The excess death associated with a high microfilarial load.* ***B:*** *The excess death associated with vision loss (blindness / visual impairment).* ***C:*** *The total excess death associated with onchocerciasis. The red, blue and green lines correspond, respectively, to a baseline endemicity of 80%, 60% and 40% microfilarial prevalence. Assumptions are as in the legend of Figure 3.2. The commencement of the intervention at year 1 is represented by the vertical dashed lines. The initially delayed decrease of excess mortality is due to a 2-year lag between incidence of death in the present and microfilarial load in the past.*

3.4.3. Impact of ivermectin on onchocerciasis disease burden

Morbidity:

Model outputs indicate that long-term annual distribution of ivermectin has an enormous impact on the morbidity associated with onchocerciasis (Figure 3.4). Two years into the programme, the incidence of blindness (associated with lagged microfilarial load) is projected to fall to very low levels (Figure 3.6). By contrast, the proportion of individuals with blindness and visual impairment due to onchocerciasis would decline more gradually, as prevalent cases are progressively removed due to host mortality (but not replaced at the same pre-control incidence level). Model results suggest a very strong initial decline in the prevalence of troublesome itch due to the therapeutic benefit of ivermectin on cutaneous

pathologies (Brieger *et al.* 1998b), followed by a more steady decline during the programme due to a gradual reduction in transmission (and prevalence of adult female worms), the magnitude of which depends on pre-control endemicity level (the higher the level the lower the rate of decrease).

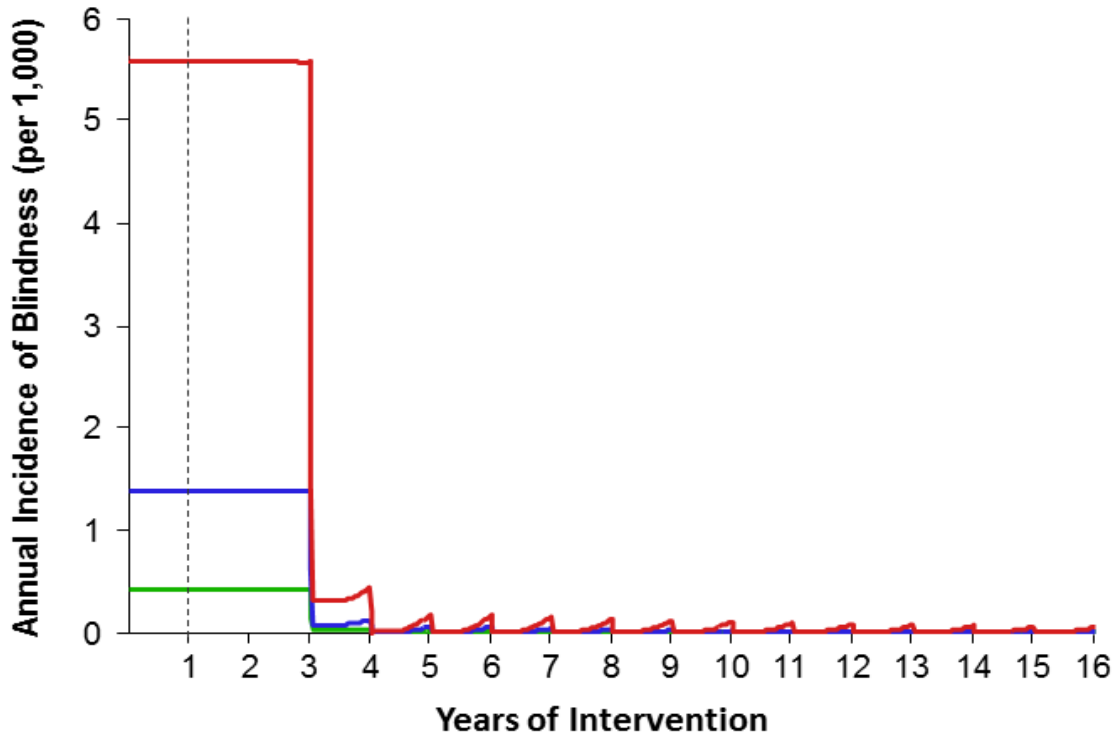

Figure 3.6. Impact of annual ivermectin distribution on incidence of blindness due to onchocerciasis in savannah areas of Africa. *The red, blue and green lines correspond, respectively, to a baseline endemicity of 80%, 60% and 40% microfilarial prevalence. The commencement of the intervention at year 1 is represented by the vertical dashed line. The initially delayed decrease is due to a 2-year lag between blindness incidence in the present and microfilarial load in the past. Results shown assume a therapeutic coverage of 80%, 0.1% of systematic non-compliance, perennial transmission, and a 7% cumulative reduction in microfilarial production by female adult worms per ivermectin dose.*

Excess Mortality:

Under ivermectin distribution the incidence of excess mortality associated with high microfilarial load is projected to decrease rapidly to low levels (Figure 3.5A). The decline is delayed by two years after the start of ivermectin distribution because of the assumption in

the model that the incidence of excess mortality due to infection is associated not with present microfilarial load but that with that experienced two years in the past (Little *et al.* 2004b). The incidence of excess mortality associated with onchocercal related vision loss decreases at a slower rate, following the decline in the prevalence of vision loss (Figure 3.5B). Figure 3.5C represents the total excess mortality due to onchocerciasis.

3.4.4. Impact of programmatic variables: therapeutic coverage and compliance patterns

Varying in the model the levels of therapeutic coverage in the overall population and the proportion of systematic non-compliers influences the projected impact of long-term ivermectin distribution on microfilarial prevalence and intensity. An increased level of overall therapeutic coverage (from 60% to 80%), or an increased level of treatment compliance (a decreased proportion of systematic non-compliers, from 5% to 0.1%) decreased the output values of microfilarial prevalence and intensity measured 1 year after the 15th annual treatment (Tables 3.3 and 3.4). By and large, the proportional reductions in infection due to improved coverage or compliance are greater in magnitude for the meso- and hyperendemic levels than for the highly hyperendemic level. The proportional reductions of onchocerciasis-associated disease burden gained as a result of improved coverage and compliance were generally relativity small in comparison.

Table 3.3. The effect of annual ivermectin treatment coverage on the microfilarial prevalence and intensity of onchocerciasis and its associated morbidity and mortality according to baseline endemicity

Pre-control endemicity	**Mesoendemic**			**Hyperendemic**			**Highly hyperendemic**		
Therapeutic coverage	**60%**	**80%**	**%[†] change**	**60%**	**80%**	**%[†] change**	**60%**	**80%**	**%[†] change**
Skin microfilarial prevalence (%)	3.46	1.84	47%	9.52	4.74	50%	27.53	16.69	39%
Microfilarial intensity (Mf/mg)	1.08	0.49	55%	3.10	1.31	58%	11.14	5.47	51%
Blindness prevalence (%)	0.299	0.297	0.67%	0.95	0.91	4%	4.25	4.13	3%
Visual impairment prevalence (%)	0.4015	0.4014	0.02%	1.27	1.22	4%	5.7	5.54	3%
Troublesome itch prevalence (%)	5.57	3.59	36%	10.94	7.45	32%	17.9	14.51	19%
Excess mortality annual incidence (per 1000)	0.09	0.08	11%	0.29	0.26	10%	1.39	1.13	19%

Values correspond to model outputs 12 months after the 15th annual ivermectin treatment assuming perennial transmission, 0.1% of systematic non-compliance and a 7% cumulative, per ivermectin dose, reduction in the rate of microfilarial production by adult female worms. Intensity of infection is quantified as mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years. Pre-control microfilarial prevalence as in Table 3.1.[†] Proportional (percent) reduction in parasitological, morbidity and mortality indicators relative to the lower (60%) treatment coverage of the total population (overall therapeutic coverage).

Table 3.4. The effect of the proportion of systematic non-compliance with annual ivermectin treatment on the microfilarial prevalence and intensity of onchocerciasis infection and its associated morbidity and mortality according to baseline endemicity

Pre-control endemicity	**Mesoendemic**			**Hyperendemic**			**Highly hyperendemic**		
Systematic non-compliance	**5%**	**0.1%**	**%† change**	**5%**	**0.1%**	**%† change**	**5%**	**0.1%**	**%† change**
Skin microfilarial prevalence (%)	2.60	1.84	29%	6.68	4.74	29%	20.08	16.69	17%
Microfilarial intensity(Mf/mg)	0.80	0.49	39%	2.20	1.31	40%	8.18	5.47	33%
Blindness prevalence (%)	0.299	0.297	1%	0.95	0.91	4%	4.26	4.13	3%
Visual impairment prevalence (%)	0.41	0.40	2%	1.27	1.22	4%	5.70	5.54	3%
Troublesome itch prevalence (%)	4.44	3.59	19%	8.88	7.45	16%	15.40	14.51	6%
Excess mortality annual incidence (per 1000)	0.09	0.08	11%	0.30	0.26	13%	1.29	1.13	12%

Values correspond to model outputs 12 months after the 15th annual ivermectin treatment assuming perennial transmission, an overall treatment coverage of 80% (high coverage), and a 7% cumulative, per ivermectin dose, reduction in the rate of microfilarial production by adult female worms. Intensity of infection is quantified as mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years. Pre-control microfilarial prevalence as in Table 3.1. † Proportional (percent) reduction in parasitological, morbidity and mortality indicators relative to the higher (5%) proportion of systematic non-compliance.

3.4.5. Impact of the efficacy of ivermectin anti-macrofilarial action

The magnitude of the assumed anti-macrofilarial action of ivermectin (i.e. the per dose proportion by which microfilarial production by female worms is cumulatively reduced) influenced the long-term impact of annual ivermectin distribution on microfilarial prevalence and intensity. The higher value (30%) had a more pronounced effect than the lower (7%) value (Figure 3.7 in comparison to Figure 3.2). However, this effect also depended on the baseline level of onchocerciasis endemicity; the lower the pre-control endemicity, the smaller the impact of assuming the stronger anti-macrofilarial effect (Table 3.5). By contrast, the assumed value of this effect had little influence regarding the impact of annual ivermectin MDA on onchocerciasis-associated disease burden (Table 3.5).

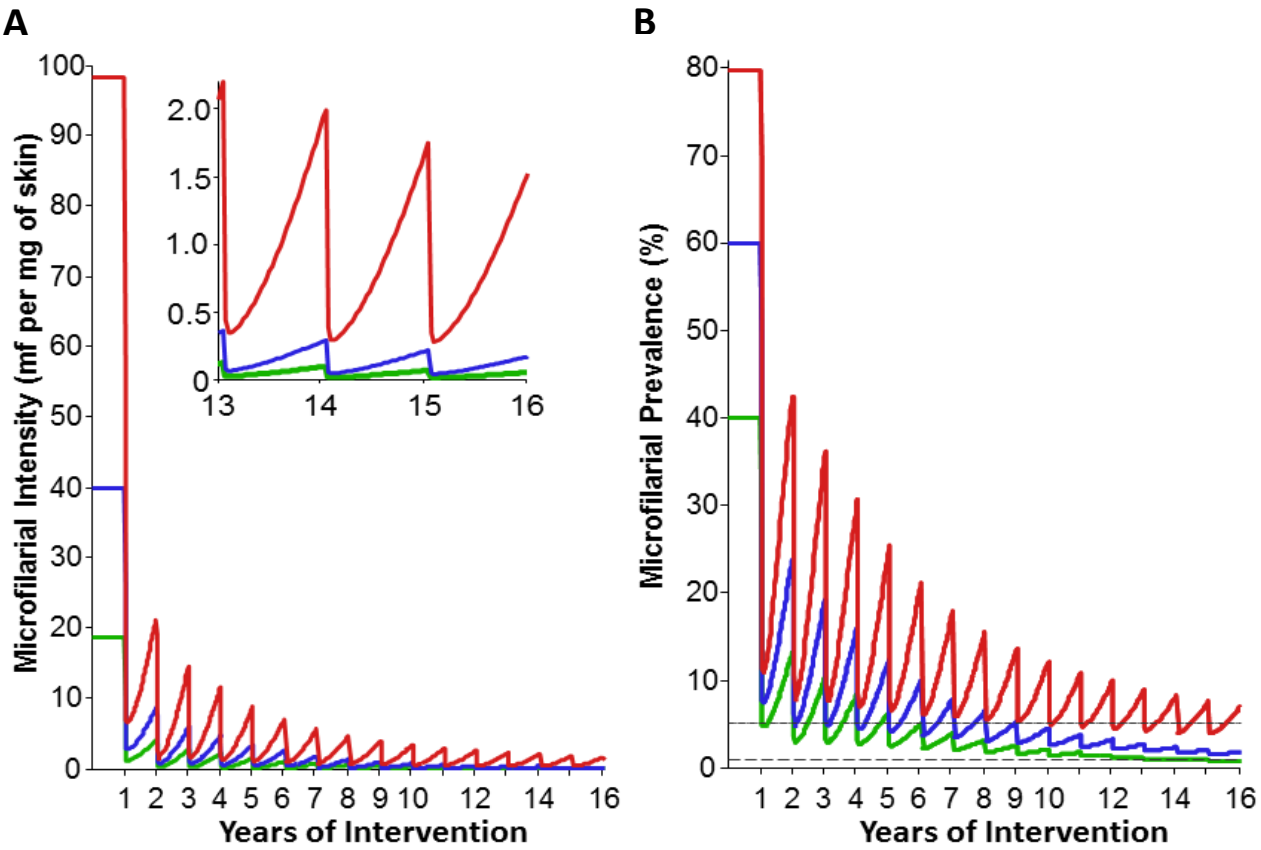

Figure 3.7. Impact of annual ivermectin distribution on microfilarial intensity (A) and microfilarial prevalence (B) when assuming a stronger anti-macrofilarial action. *The red, blue and green lines correspond, respectively, to a baseline endemicity of 80%, 60% and 40% microfilarial prevalence. Microfilarial intensity is quantified as the mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years. The dashed horizontal lines illustrate the upper and lower bounds (5% and 1% prevalence) of the current operational thresholds for cessation of treatment, namely an observed a microfilarial prevalence below 5% in all surveyed villages and 1% in 90% of the surveyed villages) (African Programme for Onchocerciasis Control, 2010). Results shown assume a therapeutic coverage of 80%, 0.1% of systematic non-compliance, perennial transmission, and a 30% cumulative reduction in microfilarial production by female adult worms per ivermectin dose. The inset in Figure 3.7A zooms in microfilarial infection intensity (in the ≥20 yr of age) for the last four years of the simulated intervention programme.*

Table 3.5. The effect of the magnitude of the anti-macrofilarial action of ivermectin on the microfilarial prevalence and intensity of onchocerciasis infection and its associated morbidity and mortality according to baseline endemicity

Pre-control endemicity	**Mesoendemic**			**Hyperendemic**			**Highly hyperendemic**		
Cumulative per dose reduction in Mf production	**7%**	**30%**	**%† change**	**7%**	**30%**	**%† change**	**7%**	**30%**	**%† change**
Skin microfilarial prevalence (%)	1.84	0.78	58%	4.74	1.80	62%	16.69	6.92	59%
Microfilarial intensity (Mf/mg)	0.49	0.06	88%	1.31	0.19	85%	5.47	1.59	71%
Blindness prevalence (%)	0.297	0.296	0.3%	0.913	0.910	0.3%	4.13	4.12	0.2%
Visual impairment prevalence (%)	0.40	0.39	2.5%	1.223	1.221	0.2%	5.54	5.52	0.4%
Troublesome itch prevalence (%)	3.59	2.67	26%	7.45	5.41	27%	14.51	12.99	10%
Excess mortality annual incidence (per 1000)	0.0818	0.0815	0.4%	0.26	0.25	4%	1.13	1.10	3%

Values correspond to model outputs 12 months after the 15th annual ivermectin treatment assuming perennial transmission, an overall treatment coverage of 80% (high coverage), and 0.1% of systematic non-compliance). Intensity of infection is quantified as mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years. Pre-control microfilarial prevalence as in Table 3.1.† Proportional (percent) reduction in parasitological, morbidity and mortality indicators relative to the lower (7%) cumulative reduction in the rate of microfilarial production by adult female worms.

3.5. Discussion

3.5.1. The influence of the epidemiological setting

Impact of Ivermectin on Microfilarial Prevalence and Intensity:

The benefit of long-term annual ivermectin distribution on onchocerciasis prevalence and intensity was influenced by the pre-control level of endemicity. This trend is consistent with other modelling studies investigating the impact of annual ivermectin control (African Programme for Onchocerciasis Control, 2010; Duerr *et al.* 2011; Winnen *et al.* 2002). Although the projections indicate that prolonged annual ivermectin distribution reduces substantially the ocular morbidity and excess mortality associated with onchocerciasis, partly due to vast reductions in microfilarial infection intensity, its impact on the prevalence of infection (and arguably on transmission) is less pronounced. This will be the product of a combined effect of the non-linear relationship between microfilarial prevalence and intensity, and the relaxation of the density-dependent processes that affect parasite development and vector survival incorporated in the model (Basáñez *et al.* 2009). These findings are consistent with the conclusions of a review assessing the impact of repeated ivermectin MDA in the former OCP area (Borsboom *et al.* 2003), highlighting that although the disease burden associated with onchocerciasis will certainly be reduced to very low levels, likely leading to the elimination (or near elimination) of the public health burden of the disease, continued drug distribution as well as sustained efforts to keep high levels of treatment coverage and compliance, will be vital to interrupt transmission and lead to elimination of the infection reservoir.

After 15 years of annual ivermectin MDA, with consistently high therapeutic coverage, compliance and drug efficacy, projected values of microfilarial prevalence in mesoendemic (1.8%) and hyperendemic (4.7%) areas (Figure 3.2, Table 3.3), start approaching operational thresholds for treatment interruption followed by surveillance (OTTIS) proposed by APOC (African Programme for Onchocerciasis Control, 2010). (These thresholds include a microfilarial prevalence lower than 5% in all surveyed villages and lower than 1% in 90% of these.) Therefore, the model's projections are consistent with those obtained in epidemiological surveys in Mali, Senegal and Nigeria after 15–17 years of ivermectin distribution (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012).

However, projected reductions in microfilarial prevalence and intensity were less optimistic for higher levels of the hyperendemicity range (80% initial microfilarial prevalence). In such settings there would be a higher rate of microfilarial reappearance in the skin between consecutive treatments as adult female worms resume microfilarial production. Although under repeated and prolonged ivermectin treatment this rebound in microfilarial intensity was found not to have severe implications for morbidity, it will make it harder to achieve the proposed OTTIS.

Now that there has been a shift in onchocerciasis control policy in Africa, from the elimination of morbidity to the elimination of infection, the dynamics of transmission during the inter-treatment periods will become increasingly relevant, highlighting the need to use mathematical models to capture and understand the underlying processes. Furthermore, the modelling results indicate that if ivermectin does not have a strong anti-macrofilarial action, elimination in highly hyperendemic areas would not be feasible with annual ivermectin MDA alone. This underscores the importance of the continued search and consideration for novel interventions and optimal combinations of currently available tools (Taylor *et al.* 2010). Potential tools include vector control, macrofilaricidal therapies, more potent microfilaricides or repositioning of current anthelmintics with different regimes and vaccines, as well as the use of transmission dynamic models with which to assess rigorously the impact of such interventions (singly or in combination) according to epidemiological, parasitological and entomological features (as done in malaria (Griffin *et al.* 2010)).

The current operational thresholds for cessation of treatment (African Programme for Onchocerciasis Control, 2010), are based on results from foci with strongly seasonal transmission and with pre-control values of microfilarial prevalence ranging from mesoendemicity to the lower end of hyperendemicity (though only 3 of 39 (8%) villages in the Mali/Senegal foci treated annually were hyperendemic (Diawara *et al.* 2009) (as defined in Table 1.1). Likewise, in the foci located in Kaduna state, Nigeria, where elimination has also been reported, the median community microfilarial load (CMFL) was only 4 Mf per skin snip (and the median baseline prevalence only 52%) (Tekle *et al.* 2012). These results advise caution when generalising conclusions regarding the feasibility of parasite elimination with annual ivermectin treatment in areas of high pre-control endemicity and perennial transmission. This emphasizes the need for evaluation and validation of the proposed OTTIS

criteria (Diawara *et al.* 2009; Traore *et al.* 2012), and the importance of not equating them with true transmission breakpoints (below which the parasite population is not able to maintain itself) (Basáñez *et al.* 2009; Duerr *et al.* 2011; Gambhir *et al.* 2009). These cautionary conclusions are supported by a range of recent epidemiological reports by Katabarwa and co-workers which provide evidence of continued transmission after more than 15 years of annual ivermectin treatment in foci of Cameroon and Uganda with high pre-control endemicity or transmission levels (Katabarwa *et al.* 2013a; Katabarwa *et al.* 2011; Katabarwa *et al.* 2013b).

Pre-control Disease Burden:

In the absence of control interventions, onchocerciasis poses a high disease burden which is non-linearly related to pre-control endemicity level. Model outputs of baseline prevalence of onchocercal related vision loss and troublesome itch in different epidemiological settings are consistent with published data (Hougard *et al.* 2001; Murdoch *et al.* 2002; Prost & Prescott, 1984; Remme *et al.* 1989). The estimated blindness rates are in good agreement with those reported prior to the commencement of interventions in the core area of the former OCP (Hougard *et al.* 2001; Prost & Prescott, 1984; Remme *et al.* 1989). However, there is heterogeneity in reports of (observed) prevalence of onchocerciasis-associated morbidity, particularly regarding the prevalence of troublesome itch (Hougard *et al.* 2001; Murdoch *et al.* 2002; Prost & Prescott, 1984; Remme *et al.* 1989).

Estimates of DALYs included the component of disease burden due to the relationship between excess host mortality of sighted individuals and heavy microfilarial load (Little *et al.* 2004b; Walker *et al.* 2012). At baseline, this contribution was greater than that of mortality associated with vision loss. The difference between the two components of premature death increased with the level of pre-control endemicity. This suggests that premature death related to onchocerciasis, and consequently its overall contribution to disease burden may be higher than previously estimated (Coffeng *et al.* 2013; Habbema *et al.* 2007; Shibuya *et al.* 2006). Furthermore, the recent values of the global disease burden of onchocerciasis (Murray *et al.* 2012), which did not include excess host mortality, are potentially underestimated.

Additionally, the relative contribution of the different disease states to the overall disease burden depends on the epidemiological setting. For example, troublesome itch is responsible

for 51% of the overall pre-control DALY burden in mesoendemic areas broadly consistent with previous estimates reporting that onchocercal itching accounts for 60% of the DALYs due to infection with *O. volvulus* (Remme *et al.* 2006). However, this proportion amounts only to 11% in the highly hyperendemic setting. By contrast, the contribution to the total DALY burden by vision loss is 28% in the mesoendemic scenario compared to 53% in the highly hyperendemic setting (Table 3.2).

Impact of Ivermectin on Onchocerciasis Disease Burden:

Prolonged annual ivermectin distribution is undoubtedly highly effective at reducing the morbidity and excess mortality associated with onchocerciasis. The projections of a steady decline in the prevalence of blindness are in line with studies investigating the long-term impact of onchocerciasis control on vision loss as well as with ONCHOSIM projections (Coffeng *et al.* 2013; Dadzie *et al*; Hougard *et al.* 2001; Prost & Prescott, 1984; Thylefors & Tonjum, 1980). However, the projected reduction in onchocercal related vision loss was not as high as that reported by Emukah *et al*. (2004), who observed a fall in prevalence from 16% to 1% (a 95% reduction) after only eight years of annual ivermectin distribution. This difference could potentially be due to a higher incidence of excess mortality than that assumed in the model being experienced by those with vision loss in the study area (Emukah *et al.* 2004). Others have assumed that four rounds of ivermectin treatment would reduce the burden of visual impairment and blindness by 35% (Remme *et al.* 2006). In the model there is no therapeutic benefit of ivermectin on (irreversible) vision loss; therefore, reductions in prevalence are due to gradual mortality of those with blindness/visual impairment. This contrasts with the faster reduction in the incidence of blindness, which reaches very low levels within a few years of ivermectin MDA (due to its pronounced effect on microfilarial load). However, onchocerciasis-related vision loss may still account for a non-negligible disease burden during on-going control programmes due to remaining prevalent cases. This aspect was not included in recent estimates of the global burden of disease due to onchocerciasis (Murray *et al.* 2012).

Model outputs indicating that the overall prevalence of troublesome itch due to onchocerciasis would roughly halve after 5–6 years of annual ivermectin treatment are consistent with data from a multi-centre trial assessing the impact of CDTI on itching and skin disease within APOC (Ozoh *et al.* 2011). This study consisted of two cross-sectional

surveys using a standardised study protocol across seven sites. Other authors have assumed that four rounds of ivermectin treatment would reduce the prevalence of troublesome itching by 85% (Remme *et al.* 2006), but this optimistic expectation is not supported by the results of Ozoh *et al.* (2011) or these modelling outputs. With the exception of two studies by Whitworth *et al.* (1996b; 1992), which concluded that ivermectin had no effect on skin disease, the projected reductions are in broad agreement with the literature (Brieger *et al.* 1998b; Kennedy *et al.* 2002; Ozoh *et al.* 2011; Somo *et al.* 1993; Whitworth *et al.* 1996a). Subsequent studies by Whitworth and colleagues using a longer time period and an improved study design, reported a reduction in troublesome itch of 30% after six years of annual ivermectin treatment (Whitworth *et al.* 1996a). The estimated impact of ivermectin on troublesome itch was slightly lower in highly hyperendemic settings, probably due to the degree of continued transmission and reinfection that takes place during inter-treatment annual ivermectin rounds.

3.5.2. The influence of programmatic and drug efficacy variables

Therapeutic Coverage and Compliance Patterns:

Varying levels of overall coverage (comparing a moderate therapeutic coverage of the total population of 60% with a higher coverage of 80%), and varying levels of systematic non-compliance (comparing 5% of individuals never taking treatment with a higher compliance of only 0.1%) had little effect on the substantial impact that regular and prolonged ivermectin treatment has on the morbidity and excess mortality associated with onchocerciasis. However, both these programmatic considerations had a marked influence on the projected impact of annual ivermectin treatment on the prevalence and intensity of microfilarial infection (Chapter 2). This indicates that under the new impetus for elimination of infection (as opposed to elimination of morbidity only) (London Declaration on Neglected Tropical Diseases, 2013; World Bank, 2012; World Health Organization, 2013), the proportion of the population that for whatever reason always refuse treatment, cannot take it, or cannot be reached will become very important in terms of achieving parasite elimination goals. Operational research efforts should be made to understand what proportion and (age- and sex-) groups of the population do not take treatment (Brieger *et al.* 2012; Brieger *et al.* 2011), what are the reasons behind this non-compliance, and how to develop effective strategies to increase treatment adherence/compliance (see Chapter 2). In addition, it will also be

important to ascertain whether and to which extent systematic non-compliers are represented in monitoring and evaluation sampling protocols, as it is conceivable that individuals who are non-compliant to treatment may not be present during parasitological assessments, biasing the results and potentially leading to erroneous decisions concerning cessation of treatment.

Anti-Macrofilarial Effect of Ivermectin:
It was assumed that ivermectin only has a relatively small anti-macrofilarial action (Bottomley *et al.* 2008; Gardon *et al.* 2002; Pion *et al.* 2013), i.e., effecting a 7% cumulative reduction on the rate of microfilarial production by adult female worms per standard dose. However, due to uncertainty in the magnitude of this effect (discussed in Chapter 2), analyses were also conducted assuming the operation of a stronger (30% per dose) anti-macrofilarial action (Plaisier *et al.* 1995). Varying the efficacy of this proposed effect of ivermectin had a prominent impact on projected microfilarial prevalence and intensity, but did not greatly affect the projected impact on disease burden. The degree to which the assumed magnitude of the anti-macrofilarial effect influenced infection model outputs decreased with decreasing pre-control endemicity, as the amount of residual transmission occurring between consecutive treatments would be considerably lower.

3.6. Conclusions

Long term annual ivermectin treatment is highly effective in reducing the morbidity and excess mortality associated with onchocerciasis. Consequently, the goals of eliminating the public health burden of onchocerciasis will most likely be met in those areas where long-term, annual ivermectin distribution is feasible. However, due to the dynamic nature of ivermectin's action on the production of microfilaria (Basáñez *et al.* 2008), these parasite stages will reappear in the skin between consecutive annual treatments; this degree of microfilarial repopulation is substantially larger in (highly) hyperendemic areas making the infection much harder to eliminate**.** This indicates the goals of eliminating the onchocerciasis infection reservoir will depend on epidemiological and programmatic variables, precluding a one-size-fits-all approach to onchocerciasis elimination in Africa.

3.7. Limitations

Currently, EpiOncho has been calibrated for savannah settings of Africa; thus, results are not necessarily directly generalisable to forest settings which have different relationships between infection and sequelae (Basáñez *et al.* 2006; Bradley *et al.* 2005; Duke, 1990), different transmission intensities (Duke *et al.* 1972), and where onchocerciasis vectors are different members of the *Simulium damnosum* s.l. complex (Dadzie *et al.* 1989) (but also see (Cheke & Garms, 2013) for a review of blindness associated with different epidemiological and entomological settings in savannah and forest areas).

The present version of the model assumes a stationary age distribution and a stable (closed) population and consequently does not account for potential effects of onchocerciasis-related excess host mortality on the population distribution or host migration. Additionally, the results presented here assume that transmission occurs all year round. Further investigation of the influence of different seasonal transmission patterns on the optimal timing of ivermectin distribution will be essential.

As in other modelling studies of the health impact of ivermectin (Coffeng *et al.* 2013), I only included disease manifestations for which data were available for model parameterisation. Consequently, the disease burden associated with several types of skin disease (such as leopard skin) (Murdoch *et al.* 2002; Ozoh *et al.* 2011) was not quantified and therefore the pre-control disease burden and the overall health impact of ivermectin may be underestimated. Furthermore, it has been suggested that onchocerciasis may be associated with epilepsy (Boussinesq *et al.* 2002; Pion *et al.* 2009) and nodding disease, as well as responsible for other neurological and hormonal involvement such as the Nakalanga syndrome (Kipp *et al.* 1996; Newell *et al.* 1997), which have not yet been included in disease models. It is clear that further work and data are required to improve assessment of the disease burden associated with onchocerciasis in future iterations of the Global Burden of Disease study.

Additionally, it is noteworthy that most disease models (including this one) are parameterised with data on sequelae collected prior to the onset of control interventions, and it is possible that relationships between infection and morbidity could be influenced by the treatment per

se. Consequently, there is some uncertainty regarding any model-derived predictions of the long-term impact of ivermectin on the dynamics of onchocercal disease.

Furthermore, it is important to note that despite their common use, DALYs do have several important limitations (King & Bertino, 2008):

- By intentionally avoiding the ‘‘patient perspective’’ the DALY weighting system ignores the local context as a modifier of disease burden.
- In an effort to avoid over counting actual life-years, the DALY scoring system does not address the reality of shared disabilities in the presence of comorbidities or concurrent infections.

In addition criticisms of the DALY framework have come from many other sectors, including objections based on philosophical and ethical concerns about its approach to quantifying and discounting the value of disabled life (King & Bertino, 2008; Reidpath *et al.* 2003).

3.8. Supporting Information for Chapter 3

This supporting text describes in full detail the onchocerciasis disease model which was developed by coupling output from the onchocerciasis transmission (EpiOncho) model (see Chapter 2)—namely the mean (arithmetic) number of Mf per mg of skin, the derived prevalence of Mf, and the derived prevalence of adult female worms—to the incidence and prevalence of onchocercal morbidity and mortality using statistically documented associations between infection and disease previously published. Details are also given on how DALYs were calculated using output from the disease model. Definitions and, where appropriate, values of parameters introduced in the text are given in Table 3.6 for the onchocerciasis disease model and Table 3.7 for the calculation of DALYs.

3.8.1. Microfilarial prevalence

As described in the previous chapter (section 2.8.4) the prevalence of skin Mf (prevalence of microfilaridermia), $\pi^{M}_{s,d}(t,a)$, at time t, in hosts of age, a; sex, s, and treatment compliance

group, *d*, was calculated as a function of microfilarial load per milligram (Mf/mg) of skin, $M_{s,d}(t,a)$, determined by the onchocerciasis transmission model,

$$\pi_{s,d}^{M}(t,a) = 1 - \left[1 + \frac{M_{s,d}(t,a)}{k_M\left[M_{s,d}(t,a)\right]}\right]^{-k_M\left[M_{s,d}(t,a)\right]}, \tag{3.1}$$

where $k_M[M_{s,d}(t,a)]$ is given by,

$$k_M\left[M_{s,d}(t,a)\right] = \frac{k_0\, M_{s,d}(t,a)}{1 + k_1\, M_{s,d}(t,a)}. \tag{3.2}$$

3.8.2. Human population

To calculate the stratum-specific population size, $P_{s,d}(a)$, the total population size, *P*, was multiplied by the proportion of individuals of sex s, q_s; age *a*, $\rho(a)$; and compliance group *d*, η_d,

$$P_{s,d}(a) = q_s \eta_d \rho(a) P \ . \tag{3.3}$$

The age and sex distributions of the population, modelled by the function $\rho(a)$ and the parameter q_s respectively, were estimated from demographic data on individuals living in the Vina Valley region of northern Cameroon (Filipe *et al.* 2005). The population structure and size were assumed to be stationary; the latter set to an arbitrary constant large enough to ensure accuracy of numerical integration.

3.8.3. Blindness

The incidence of blindness due to onchocerciasis, denoted $\nu_{s,d}(t,a)$, is given by the incidence of blindness *not* due to onchocerciasis, $\nu'_{s,d}(t,a)$ (i.e. the background incidence of blindness), subtracted from the *total* incidence of blindness, $\nu^{T}_{s,d}(t,a)$,

$$\nu_{s,d}(t,a) = \nu^{T}_{s,d}(t,a) - \nu'_{s,d}(t,a)\,. \tag{3.4}$$

The background incidence of blindness is given by the *per capita* background rate at which individuals of sex *s* and age *a* become blind (Little *et al.* 2004a), $\gamma_{0s}(a)$, multiplied by the total number of individuals who are not blind. The latter is given by subtracting the total number of blindness cases in each stratum, $B^T_{s,d}(t,a)$, from the stratum population size, $P_{s,d}(a)$,

$$\nu'_{s,d}(t,a) = \gamma_{0s}(a)\left[P_{s,d}(a) - B^T_{s,d}(t,a)\right]. \tag{3.5}$$

The total incidence of blindness in the population of sex *s* and compliance group *d* is calculated from the background incidence of blindness (Equation (3.5)) multiplied by the relative risk of blindness associated with a mean (arithmetic) number of Mf per skin snip, $r_{s,d}(t,a)$,

$$\nu^T_{s,d}(t,a) = \nu'_{s,d}(t,a) r_{s,d}(t,a). \tag{3.6}$$

Substituting $\nu'_{s,d}(t,a)$ (Equation (3.5)) and $\nu^T_{s,d}(t,a)$ (Equation (3.6)) into Equation (3.4) yields the desired expression for the incidence of blindness *due to* onchocerciasis,

$$\nu_{s,d}(t,a) = \gamma_{0s}(a)\left[r_{s,d}(t,a) - 1\right]\left[P_{s,d}(a) - B^T_{s,d}(t,a)\right]. \tag{3.7}$$

The relative risk term on the right hand side (RHS) of Equation (3.7) was calculated using a log-linear model previously fitted to data on the incidence of blindness throughout the entire duration of the OCP (Little *et al.* 2004a),

$$r_{s,d}(t,a) = \exp\left[\gamma_1 M'_{s,d}(t-2,a)\right]\pi^M_{s,d}(t-2,a). \tag{3.8}$$

Here $M'_{s,d}(t-2,a)$ denotes mean (arithmetic) microfilarial load per skin snip (as opposed to per mg of skin, see below) lagged by two years, reflecting that loss of visual acuity is associated with past microfilarial load, with the best lag estimated as 2 years (Little *et al.* 2004a). The term γ_1 on the RHS of Equation (3.8) is the regression coefficient for the relative risk of blindness associated with a microfilarial load, as estimated in Little *et al.* (2004a) (Table 3.6). The microfilarial load per skin snip was derived by multiplying the microfilarial load per mg of skin (obtained from the transmission model) by the mean (arithmetic) weight in milligrams of a skin snip sample taken from the iliac crest using a Holth-type corneoscleral

punch. This mean (arithmetic) was estimated as 1.7 mg (S.E. = 0.012) from data presented by Collins *et al*. (1992). This conversion was necessary because the OCP did not weigh the skin snips and consequently Equation 3.8 was parameterized using data on Mf per skin snip rather than per mg. The prevalence term, $\pi^{M}_{s,d}(t-2,a)$, in Equation (3.8) ensures that the relative risk of blindness *due to* onchocerciasis applies only to those who are infected.

The total number of people blind—the $B^{T}_{s,d}(t,a)$ term on the RHS of Equation (3.7) —was calculated by means of a partial differential equation comprising two (host age- and sex-dependent) rates: the total incidence of new blindness cases, $\nu^{T}_{s,d}(t,a)$ (Equation (3.6)), minus the loss due to mortality of already blinded individuals, with *per capita* rate as the product of the background mortality rate $\xi(a)$ and the excess risk of mortality associated with blindness E^{B} (Shibuya *et al.* 2006),

$$\frac{\partial B^{T}_{s,d}(t,a)}{\partial t}+\frac{\partial B^{T}_{s,d}(t,a)}{\partial a}=\nu^{T}_{s,d}(t,a)-B^{T}_{s,d}(t,a)\xi(a)E^{B}. \tag{3.9}$$

The expression for the background mortality rate, $\xi(a)$, is given in section 3.8.6. The number of blindness cases *due* to onchocerciasis, $B_{s,d}(t,a)$ (as opposed to the *total* number of blindness cases) was calculated in a similar fashion but using $\nu_{s,d}(t,a)$, the incidence of blindness *due to* onchocerciasis (Equation (3.7)),

$$\frac{\partial B_{s,d}(t,a)}{\partial t}+\frac{\partial B_{s,d}(t,a)}{\partial a}=\nu_{s,d}(t,a)-B_{s,d}(t,a)\xi(a)E^{B}. \tag{3.10}$$

The relative risk of blindness due to onchocerciasis, $r_{s,d}(t,a)$ (Equation (3.8)) was determined by analysing data where blindness was defined as a visual acuity of less than 3/60 based on tests for central vision (Little *et al.* 2004a). It does not include individuals with visual acuity equal to or better than 3/60 but who have a restriction of visual field to less than 10° of fixation. Such individuals would have been classified as blind if peripheral visual field assessment had been conducted. It has been estimated that this approach misses 25% of functional blindness cases (Remme, 2004a; World Health Organization, 1983). To account for this, the number of age- and sex-dependent blindness cases due to onchocerciasis per

stratum (given by the solution of Equation (3.10)) was multiplied by 4/3 (Coffeng *et al.* 2013; Remme, 2004a). The total number of blindness cases due to onchocerciasis was calculated by integrating over host age and summing over sex and treatment compliance strata,

$$B(t) = \frac{4}{3}\sum_{s}\sum_{d}\int_{a} B_{s,d}(t,a)\, da. \tag{3.11}$$

The prevalence of onchocercal blindness, $\pi^{B}(t)$, is calculated by dividing the total number of blindness cases by the population size, P,

$$\pi^{B}(t) = \frac{B(t)}{P}. \tag{3.12}$$

3.8.4. Visual impairment

The number of visual impairment cases, $V_{s,d}(t,a)$, was calculated using a ratio of 1.78 cases of visual impairment for every case of blindness (when blindness is defined as a visual acuity of less than 3/60 alone) (Remme, 2004a). This ratio was estimated from data collected in hyperendemic onchocerciasis foci (without adjusting for the functionally blind cases as described above), but it was assumed to hold for lower endemicity foci (Remme, 2004a). Hence,

$$V_{s,d}(t,a) = 1.78 \times B_{s,d}(t,a). \tag{3.13}$$

The prevalence of onchocercal visual impairment $\pi^{V}(t)$, is then given by,

$$\pi^{V}(t) = \frac{V(t)}{P}, \tag{3.14}$$

where,

$$V(t) = \sum_{s}\sum_{d}\int_{a} V_{s,d}(t,a)\, da. \tag{3.15}$$

The Therapeutic Effect of Ivermectin on Visual Loss:

It was assumed that both blindness and visual impairment are irreversible conditions which do not respond to ivermectin treatment. This is supported by a Cochrane review of placebo-controlled trials that found no statistically significant effect of ivermectin on prevalent vision loss (Ejere *et al.* 2001).

3.8.5. Troublesome itch

Following ONCHOSIM (Coffeng *et al.* 2013; Habbema *et al.* 2007), the baseline prevalence of troublesome itch, $\pi'^{T}_{s,d}(t)$, is defined as the prevalence of troublesome itch in the absence of ivermectin treatment. This is calculated using a previously published association between troublesome itch and the prevalence of adult female worms, $\pi^{W}_{s,d}(t)$ (Coffeng *et al.* 2013; Habbema *et al.* 2007),

$$\pi'^{T}_{s,d}(t) = \alpha_1 \left[\pi^{W}_{s,d}(t) \right] + \alpha_2 \left\{ 1 - \exp\left[\left(\pi^{W}_{s,d}(t) \right)^2 \right] \right\}, \tag{3.16}$$

where α_1 and α_2 are regression coefficients estimated by Habbema *et al.* (2007) (Coffeng *et al.* 2013) (Table 3.6). The prevalence of adult female worms $\pi^{W}_{s,d}(t)$ was calculated assuming that worms are distributed among hosts according to a negative binomial distribution with mean $W_{s,d}(t,a)$ and overdispersion parameter k_W,

$$\pi^{W}_{s,d}(t) = 1 - \left[1 + \frac{W_{s,d}(t)}{k_W} \right]^{-k_W}, \tag{3.17}$$

where $k_W = 0.35$ as estimated by Bottomley *et al.* (2008). The prevalence of troublesome itch was related to female adult worms because the association between the presence of Mf and troublesome itch does not hold during ivermectin treatment; the reduction in prevalence of itch is smaller and more delayed than the drop in microfilarial prevalence and load (Brieger *et al.* 1998b; Coffeng *et al.* 2013; Habbema *et al.* 2007).

The number of baseline troublesome itch cases per stratum, $T'_{s,d}(t)$, is the product of the baseline prevalence of troublesome itch, the proportion of individuals of each sex, q_s, compliance group, η_d, and the population size *P*,

$$T'_{s,d}(t) = \pi'^{T}_{s,d}(t) q_s \eta_d P. \tag{3.18}$$

The total number of baseline troublesome itch cases is then given by summing over the sex and compliance strata,

$$T'(t) = \sum_s \sum_d T'_{s,d}(t). \tag{3.19}$$

Therapeutic Effect of Ivermectin on Troublesome Itch:

The number of baseline cases of troublesome itch is multiplied by a factor $1-\tau_d(t)$ to yield the total number of troublesome itch cases, $T(t)$,

$$T(t) = T'(t)\left[1-\tau_d(t)\right], \tag{3.20}$$

and the prevalence of troublesome itch is given by,

$$\pi^T(t) = \frac{T(t)}{P}. \tag{3.21}$$

Parameter $\tau_d(t)$ captures the observed therapeutic effect of ivermectin in reducing the average year-round baseline prevalence of troublesome itch by 47% in individuals treated annually and by 52% in those treated biannually, an effect which was assumed to develop gradually during the first six months of the first treatment round (Brieger *et al.* 1998b) and which was consistent with the results of a multicentre study conducted by the African Programme for Onchocerciasis Control (APOC) (Ozoh *et al.* 2011). These reductions are not assumed to act cumulatively with each treatment round but rather over the timespan of ivermectin distribution. It was further assumed that individuals treated every other year experience a 10% reduction in troublesome itch in the year they are not treated, due to the residual effects of ivermectin on cutaneous pathologies. This was estimated by the difference between the reduction of itch prevalence at 12 and 15 months after a single treatment and assumes the rate of recovery is constant from 15 months onwards (Brieger *et al.* 1998b). Long-term reductions in the prevalence of troublesome itch are not just caused by the therapeutic activity of ivermectin but rather by its community-level suppression of transmission which leads to a gradual decrease in the prevalence of adult female worms.

3.8.6. Excess mortality

The excess mortality due to onchocerciasis is assumed to occur via two processes; an additional risk of mortality among individuals suffering from onchocerciasis-related vision loss (Kirkwood *et al.* 1983; Shibuya *et al.* 2006), and an additional risk of mortality (independent of the former) among infected individuals with high microfilarial loads (Little *et al.* 2004b; Walker *et al.* 2012). To calculate the incidence of (excess) mortality associated with onchocerciasis these additional risks were multiplied by the age-specific background mortality (hazard) rate, $\xi(a)$,

$$\xi(a) = -\frac{d}{da}\ln\left[\varepsilon(a)\right], \tag{3.22}$$

where $\varepsilon(a)$ is the survivorship function,

$$\varepsilon(a) = \begin{cases} \exp(-\omega_1 a) & \text{for } a < 5\text{years}, \\ \omega_2 + \omega_3 a^2 + \omega_4 a & \text{for } a \geq 5\text{years}. \end{cases} \tag{3.23}$$

The regression coefficients $\omega_1, \omega_2, \omega_3$ and ω_4 were estimated by fitting $\varepsilon(a)$ to the same data that were used to parameterise the host survivorship function in ONCHOSIM (Habbema *et al.* 1996) (Figure 3.8). This makes my estimates of the excess mortality due to onchocerciasis comparable with other modelling studies.

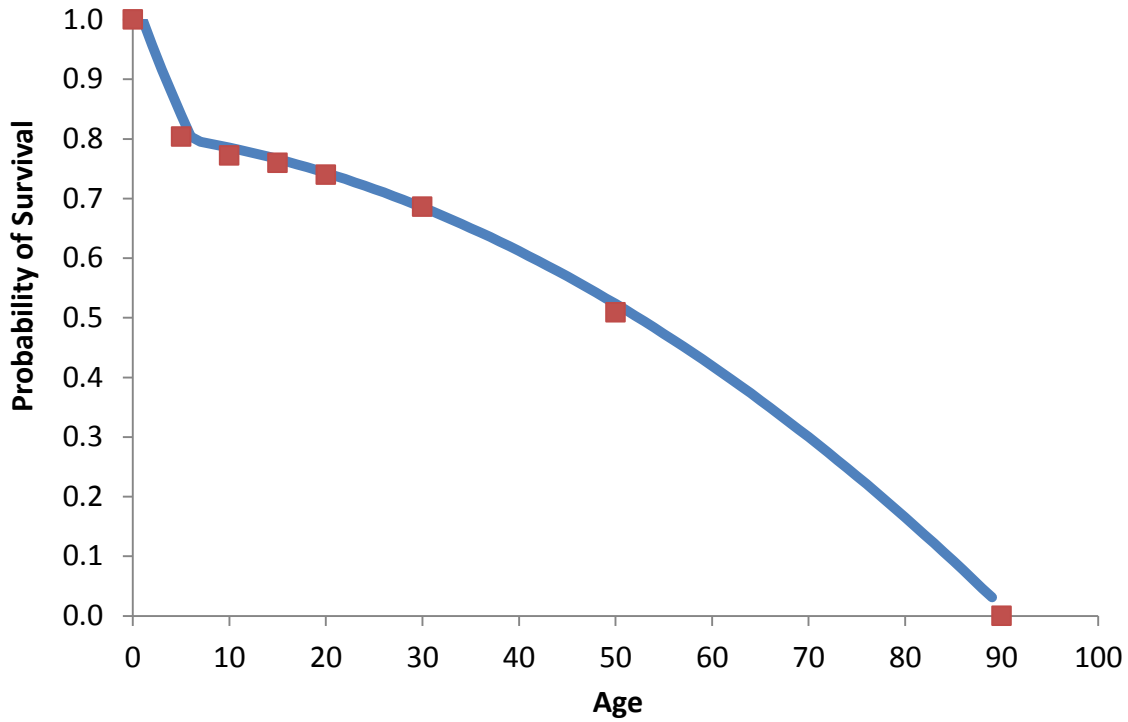

Figure 3.8. Human host survivorship function. *The blue line represents the fitted model (Equation (3.23)) and the red squares the host survivorship data (proportion of hosts surviving to a particular age) presented in Habbema et al. (1996). The model was fitted using non-linear least squares regression yielding parameter estimates* $\omega_1 = 0.04$, $\omega_2 = 0.81$, $\omega_3 = -7.7\times10^{-5}$ *and* $\omega_4 = 2.1\times10^{-3}$ *(Table 3.6).*

Excess Mortality Associated with Vision Loss:

It was assumed that the relative risk of mortality among blind individuals, E^B, and among those with visual impairment, E^V, were, respectively, 2.5 and 1.5 according to (Shibuya *et al.* 2006). The incidence of excess mortality associated with blindness, $D^B_{s,d}(t,a)$ and visual impairment, $D^V_{s,d}(t,a)$ are given by,

$$D^B_{s,d}(t,a) = B_{s,d}(t,a)\xi(a)\left(E^B - 1\right), \tag{3.24}$$

and

$$D^V_{s,d}(t,a) = V_{s,d}(t,a)\xi(a)\left(E^V - 1\right). \tag{3.25}$$

By analogy with the derivation of the incidence of blindness due to onchocerciasis given by Equations (3.4) to (3.7), the minus 1 term on the RHS of Equation (3.25) and Equation (3.26) adjusts the relative risks to give the incidence of mortality *due to* onchocerciasis, as opposed to the *total* incidence of mortality.

Excess Mortality Associated with Microfilarial Load:

A density-dependent association has been quantified between excess human mortality and microfilarial load (Little *et al.* 2004b; Walker *et al.* 2012). This was incorporated into the model using a published non-linear, host age-dependent association between the relative risk of mortality, $E^{M}_{s,d}(t,a)$, in those infected (but without vision loss) and their past (lagged by two years) microfilarial load per skin snip denoted as $M'_{s,d}$, as opposed to $M_{s,d}$ for Mf/mg, see also Equation (3.8),

$$E^{M}_{s,d}(t,a) = \exp\left\{ f\left[M'_{s,d}(t-2,a)\right] a^{\beta_4} \right\} \pi^{M}_{s,d}(t-2,a). \tag{3.26}$$

Here $f\left[M'_{s,d}(t-2,a)\right]$ describes a sigmoid functional form,

$$f\left[M'_{s,d}(t-2,a)\right] = \frac{\beta_1 M'_{s,d}(t-2,a)^{\beta_3}}{1+\beta_2 M'_{s,d}(t-2,a)^{\beta_3}}, \tag{3.27}$$

where $\beta_1, \beta_2, \beta_3$ and β_4 are regression parameters as estimated in Walker *et al.* (2012) (Table 3.6). The prevalence term in Equation (3.26), $\pi^{M}_{s,d}(t-2,a)$, ensures that the relative risk of excess mortality associated with high microfilarial load only applies to those infected and not to the whole population.

The incidence of excess mortality associated with the mean (arithmetic) number of Mf per skin snip, $D^{M}_{s,d}(t,a)$, is given by

$$D^{M}_{s,d}(t,a) = \left\{ P_{s,d}(a) - \left[B_{s,d}(t,a) + V_{s,d}(t,a) \right] \right\} \xi(a) \left[E^{M}_{s,d}(t,a) - 1 \right]. \tag{3.28}$$

The term $P_{s,d}(a) - \left[B_{s,d}(t,a) + V_{s,d}(t,a) \right]$ on the RHS of Equation (3.28) ensures that the incidence of excess mortality does not apply to prevalent cases of blindness or visual

impairment; such individuals suffer a separate excess risk of mortality as described by Equation (3.24) and Equation (3.25).

Total Incidence of Excess Mortality:

The total incidence of excess mortality aassociated with onchocerciasis—either via blindness (Equation (3.24)), visual impairment (Equation (3.25)) or via the direct association with microfilarial load (Equation (3.28))—is the sum of the component incidence rates,

$$D_{s,d}(t,a) = D^{B}_{s,d}(t,a) + D^{V}_{s,d}(t,a) + D^{M}_{s,d}(t,a) \; . \tag{3.29}$$

3.8.7. Disability adjusted life years

Disability-adjusted life years (DALYs) are a time-based measure of disease burden accounting for years lived with disability (YLDs) and years of life lost (YLLs) due to premature mortality (Murray & Lopez, 1994).

The YLDs were calculated by multiplying the number of cases of blindness, visual impairment and troublesome itch by their respective disability weights h^{B}, h^{V}, h^{T} (World Health Organization, 2004),

$$\text{YLDs}(t) = B(t)h^{B} + V(t)h^{V} + T(t)h^{T} \; . \tag{3.30}$$

The YLLs were calculated using the 'period expected years of life lost' method (World Health Organization, 2003), where the duration of life lost is the local future life-expectancy of individuals at each age, $\Xi(a)$, minus there current age, multiplied by the incidence of mortality, $D_{s,d}(t,a)$,

$$\text{YLLs}(t) = \sum_{s}\sum_{d}\int_{a}\left[\Xi(a) - a\right] D_{s,d}(t,a)\,da \tag{3.31}$$

The age-specific future life-expectancy is derived directly from the host survivorship function, $\varepsilon(a)$,

$$\Xi(a) = \frac{\int_{u=a}^{u=\infty} \varepsilon(u)\, du}{\varepsilon(a)} . \tag{3.32}$$

The YLLs were discounted at a rate of 3% per year in line with WHO guidelines (World Health Organization, 2003).

The total DALY burden is the sum of YLDs and the YLLs,

$$\mathrm{DALYs}(t) = \mathrm{YLDs}(t) + \mathrm{YLLs}(t) . \tag{3.33}$$

In line with the methodology outlined in the Disease Control Priorities Project: Priorities in Health report (Disease Control Priorities Project, 2006), I did not apply any age weighting (whereby healthy life lived at younger and older ages is given a lower weight than that at productive adult ages) to the DALYs estimates (Disease Control Priorities Project, 2006). Definitions and values of parameters are given in Table 3.7.

Table 3.6. Definition and values of parameters and variables for the onchocerciasis disease model

Symbol	Definition of variables and parameters	Expression, average value and units
	Infection & demography	
$\pi_{s,d}^{M}(t,a)$	Microfilarial prevalence at time (*t*) and age (*a*); subscript *s* denotes host sex and subscript *d* denotes treatment compliance category	Equation (3.1)
$M_{s,d}(t,a)$	Mean (arithmetic) number of microfilariae per milligram of skin at time (*t*) and age (*a*); subscripts *s* and *d* as above	*Derived from transmission model (see Chapter 2)*
$k_M[M_{s,d}(t,a)]$	Inverse measure of the degree of overdispersion in the distribution of skin microfilariae as a function of the mean (arithmetic) microfilarial load at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.2)
k_0 k_1	Parameters determining the shape of the relationship between k_M and skin microfilarial load (Equation (S.2))	0.013 0.024
η_d	Proportion of the host population in treatment compliance group *d*	–
q_s	Proportion of the host population of sex *s* (Filipe *et al.* 2005)	0.45/0.55
$\rho(a)$	Truncated exponential probability density function of host age (*a*) (Filipe *et al.* 2005)	$\frac{\mu_H \exp(-\mu_H a)}{1-\exp(-\mu_H a_m)}$
μ_H	The net rate of population loss (due to death, emigration and other process) determining the age distribution of the population (Filipe *et al.* 2005)	0.04 yr^{-1}
a_m	Maximum recorded human age in the reference population of northern Cameroon (Filipe *et al.* 2005)	80 yr
P	Total population size for accuracy of numerical integration	100,000

Table 3.6. Continued

Symbol	Definition of variables and parameters	Expression, average value and units
	Blindness	
$\nu_{s,d}(t,a)$	Incidence of blindness due to onchocerciasis at time (*t*) and age (*a*); subscript *s* denotes host sex and subscript *d* denotes treatment compliance category	Equation (3.4)
$\nu'_{s,d}(t,a)$	The background incidence of blindness at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.5)
$\nu^{T}_{s,d}(t,a)$	The total incidence of blindness at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.6)
$r_{s,d}(t,a)$	Relative risk of blindness incidence at time (*t*) and age (*a*); subscripts *s* and *d* as above (Little *et al.* 2004a)	Equation (3.8)
γ_1	Microfilarial load regression coefficient for the relative risk of blindness incidence (Little *et al.* 2004a)	1×10^{-2}
$\gamma_{0_S}(a)$	Background incidence of blindness i.e. incidence of blindness not associated with onchocerciasis at age (*a),* subscript *s* denotes host sex (Little *et al.* 2004a)	–
$M'_{s,d}(t,a)$	Mean (arithmetic) number of microfilariae per skin snip (with an average skin snip sample weight of 1.7mg (Collins *et al.* 1992)) at time (*t*) and age (*a*); subscripts *s* and *d* as above	–
$B^{T}_{s,d}(t,a)$	The total number of blindness cases at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.9)
$B_{s,d}(t,a)$	Number of blindness cases due to onchocerciasis at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.10)
$\pi^{B}(t)$	Overall prevalence of blindness due to onchocerciasis at time (*t*)	Equation (3.12)
	Visual impairment	
$V_{s,d}(t,a)$	Number of visual impairment cases due to onchocerciasis at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.13)
$\pi^{V}(t)$	Prevalence of visually impairment due to onchocerciasis at time (*t*)	Equation (3.14)

Table 3.6. Continued

Symbol	Definition of variables and parameters	Expression, average value and units
	Troublesome itch	
$\pi'^{T}_{s,d}(t)$	Baseline prevalence of troublesome itch due to onchocerciasis at time (*t*); subscript *s* denotes host sex and subscript *d* denotes treatment compliance category (Coffeng *et al.* 2013; Habbema *et al.* 2007)	Equation (3.16)
$\pi^{w}_{s,d}(t)$	Prevalence of females worms at time (*t*); subscripts *s* and *d* as above	Equation (3.17)
α_1 α_2	Coefficients describing the shape of the relationship between troublesome itch and female adult worms (Coffeng *et al.* 2013; Habbema *et al.* 2007)	-0.043 -0.46
$W_{s,d}(t)$	Mean (arithmetic) number of female adult worms per person at time (*t*); subscripts *s* and *d* as above	*Derived from transmission model (see Chapter 2)*
k_w	Inverse measure of degree of overdispersion in the distribution of female worms among hosts (Bottomley *et al.* 2008)	0.35
$T'_{s,d}(t)$	Number of baseline cases of troublesome itch due to onchocerciasis at time (*t*); subscripts *s* and *d* as above	Equation (3.18)
$T(t)$	Number of cases of troublesome itch due to onchocerciasis at time (*t*)	Equation (3.20)
$\tau_d(t)$	Average year-round reduction in the prevalence of itch associated with annual ivermectin at time (*t*); subscript *d* denotes treatment compliance category (Brieger *et al.* 1998b)	See section 3.8.5.
$\pi^{T}(t)$	Prevalence of troublesome itch due to onchocerciasis at time (*t*)	Equation (3.21)

Table 3.6. Continued

Symbol	Definition of variables and parameters	Expression, average value and units
	Excess Mortality	
$\xi(a)$	Per capita background death rate of humans at age (*a*)	Equation (3.22)
$\mathcal{E}(a)$	Host survivorship function (Habbema *et al.* 1996)	Equation (3.23)
ω_1	Regression coefficients for the host survivorship function	0.04
ω_2		0.81
ω_3		-7.7×10^{-5}
ω_4		-0.0021
E^B	The relative risk of mortality associated with blindness (Shibuya *et al.* 2006)	2.5
E^V	The relative risk of mortality associated with visually impairment (Shibuya *et al.* 2006)	1.5
$D^B_{s,d}(t,a)$	Incidence of excess mortality due to blindness at time (*t*) and age (*a*); subscript *s* denotes host sex and *d* denotes treatment compliance category	Equation (3.24)
$D^V_{s,d}(t,a)$	Incidence of excess mortality due to visual impairment at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.25)
$E^M_{s,d}(t,a)$	The relative risk of mortality associated with high microfilarial loads at time (*t*) and age (*a*); subscripts *s* and *d* as above (Walker *et al.* 2012)	Equation (3.26)
$f[M'_{s,d}(t-2,a)]$	Function describing the relationship between relative risk of mortality and microfilarial load per skin snip; subscripts *s* and *d* as above (Walker *et al.* 2012)	Equation (3.27)
β_1	Regression coefficients of the function describing the relative risk of mortality associated with high microfilarial loads(Walker *et al.* 2012)	1.8
β_2		1.8
β_3		2.5
β_4		-0.59
$D^M_{s,d}(t,a)$	Incidence of excess mortality associated with high microfilarial loads at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.28)
$D_{s,d}(t,a)$	Incidence of excess mortality due to onchocerciasis at time (*t*) and age (*a*); subscripts *s* and *d* as above	Equation (3.29)

Table 3.7. Definition and values of parameters for the disability adjusted life years estimates

Symbol	Definition of variables and parameters	Expression, average value and units
h^B	Blindness disability weight (World Health Organization, 2004)	0.59
h^V	Visual impairment disability weight (World Health Organization, 2004)	0.17
h^T	Troublesome itching disability weight (World Health Organization, 2004)	0.068
$\mathrm{YLDs}(t)$	Years lived with disability due to onchocerciasis at time (*t*)	Equation (3.30)
$\mathrm{YLLs}(t)$	Years of life lost due to onchocerciasis at time (*t*)	Equation (3.31)
$\Xi_{(a)}$	Age specific life expectancy at age (*a*) (Habbema *et al.* 1996)	Equation (3.32)
$\mathrm{DALYs}(t)$	Disability adjusted life years burden due to onchocerciasis at time (*t*)	Equation (3.33)

Chapter 4: The Cost of Annual versus Biannual Treatment with Ivermectin

4.1 Summary

Recently it has come under consideration to change from annual biannual (twice yearly) ivermectin distribution strategy is some African foci, which has been shown in Latin Africa to have the potential to interrupt transmission. However, relatively few communities have received biannual treatments in Africa. Consequently there are no cost data associated with increasing ivermectin treatment frequency at a large scale, essential pre-requisites to provide reliable information for evidence-based decision making regarding adoption of a biannual treatment strategy. This chapter describes the results of study undertaken to estimate costs associated with biannual compared to annual ivermectin delivery in Ghana, which since 2009 has implemented a biannual treatment strategy in selected priority areas. The costing data were collected as part of a field work project, conducted in January-February 2012, in collaboration with the Council for Scientific and Industrial Research, Ghana. The results indicate that the cost of biannual ivermectin treatment per year is approximately 60% higher than the cost of annual treatment. In addition, large-scale mass biannual treatment was reported as being well received by communities and health workers, and considered sustainable in the context of the Ghanaian NTD control programme This study provides tangible evidence of the different costs associated with annual and biannual ivermectin treatment, which can be used to inform economic evaluations and policy decisions regarding the optimal treatment frequency required to eliminate onchocerciasis in Africa.

A modified version of this chapter has been is published: Turner, H.C., Osei-Atweneboana, M.Y., Walker, M., Tettevi, E.J., Churcher, T.S. Asiedu, O., Biritwum, N-K. and Basáñez, M-G. (2013) The cost of annual versus biannual community-directed treatment of onchocerciasis with ivermectin: Ghana as a case study. *PLoS Negl Trop Dis,* 7(9): e2452. (See Appendix A)

4.2. Introduction

It is thought that switching from annual to biannual mass community directed treatment with ivermectin (CDTI) might improve the chances of onchocerciasis elimination in circumscribed African foci. However, in the past only a small number of foci (such as River Gambia in Senegal (Diawara *et al.* 2009)) have received biannual treatment in Africa, and therefore there are no ground-truth data on the cost associated with increasing the treatment frequency to twice per year on a large scale. In Uganda, the cost of biannual CDTI was simply estimated by doubling that of the annual treatment (Ndyomugyenyi *et al.* 2007). To perform economic evaluations of increasing the treatment frequency, it is vital to understand how the costs of treatment change and to evaluate if any complications arise from using the higher frequency.

Some countries such as Ghana (in the former Onchocerciasis Control Programme in West Africa (OCP)), and Uganda (in the African Programme for Onchocerciasis Control (APOC)), have recently adopted a biannual treatment strategy at a large scale; the former because of suspected suboptimal responses to ivermectin treatment (Osei-Atweneboana *et al.* 2007), and the latter because, in combination with vector control, elimination may be accelerated (Ministry of Health, Republic of Uganda, 2007). In this chapter, I report the results of a study undertaken to estimate the costs associated with annual (the standard strategy) vs. biannual CDTI (the newly adopted strategy) in Ghana. Furthermore, given that other countries in the region may be considering switching from annual to biannual ivermectin distribution, potential factors that may hamper the scaling up of treatment frequency at a large scale were also assessed. The data were collected as part of a field work project conducted in January-February 2012, in collaboration with the Council for Scientific and Industrial Research, Ghana.

4.3. Methods

4.3.1. Description of study areas

In Ghana, onchocerciasis is endemic in 9 out of 10 regions with a total at-risk population of approximately 3.2 million (Taylor *et al.* 2009). Responsibility for ivermectin distribution

(which occurs in 73 districts) was devolved from the OCP to Ghana in 2002 (under the supervision of APOC). Since 2006, onchocerciasis control has been implemented in the context of a Neglected Tropical Diseases Programme (NTDP) (Taylor *et al.* 2009), and in 2009, 40 (55%) districts started using a biannual ivermectin distribution strategy. The decision regarding which areas should change to the biannual treatment strategy was based on the combined results of rapid epidemiological mapping of onchocerciasis (REMO) conducted in Ghana in 2009, parasitological evaluation via skin snipping and determination of microfilarial prevalence, and entomological evaluations (according to unpublished results of the Ghana onchocerciasis mapping exercise conducted in 2009). Areas with an infection prevalence in the adults above 20%, were allocated to a biannual treatment frequency considering also a buffer zone of 20 Km around these CDTI priority areas. Therefore, NTDP decisions as to whether to allocate districts to annual or biannual CDTI were not made on a priori criteria of associated costs but only based on transmission criteria.

The study focused on the Brong-Ahafo and Northern regions in Ghana (Figure 4.1). In the former, data were collected in the Wenchi district where CDTI takes place annually; the Pru district and the Kintampo North district, where CDTI is taking place biannually, and in the latter, data were also collected in the Kpandai district, where a mixed strategy (some communities being treated annually and others biannually) is used (Table 4.1). These districts were selected partly based on logistics at the time of the study, and partly because already established relationships with the Ghana Health Service (GHS) at the district and sub-district levels would ensure collection of accurate data via the purposely designed questionnaires (Appendix B). Figure 4.1 shows the locations of the districts where the study was conducted. As stated earlier, decisions to switch to a biannual treatment frequency were based on infection and transmission criteria alone, so there were no obvious reasons why the decision to change treatment frequency would have been influenced by the local district-specific programme cost.

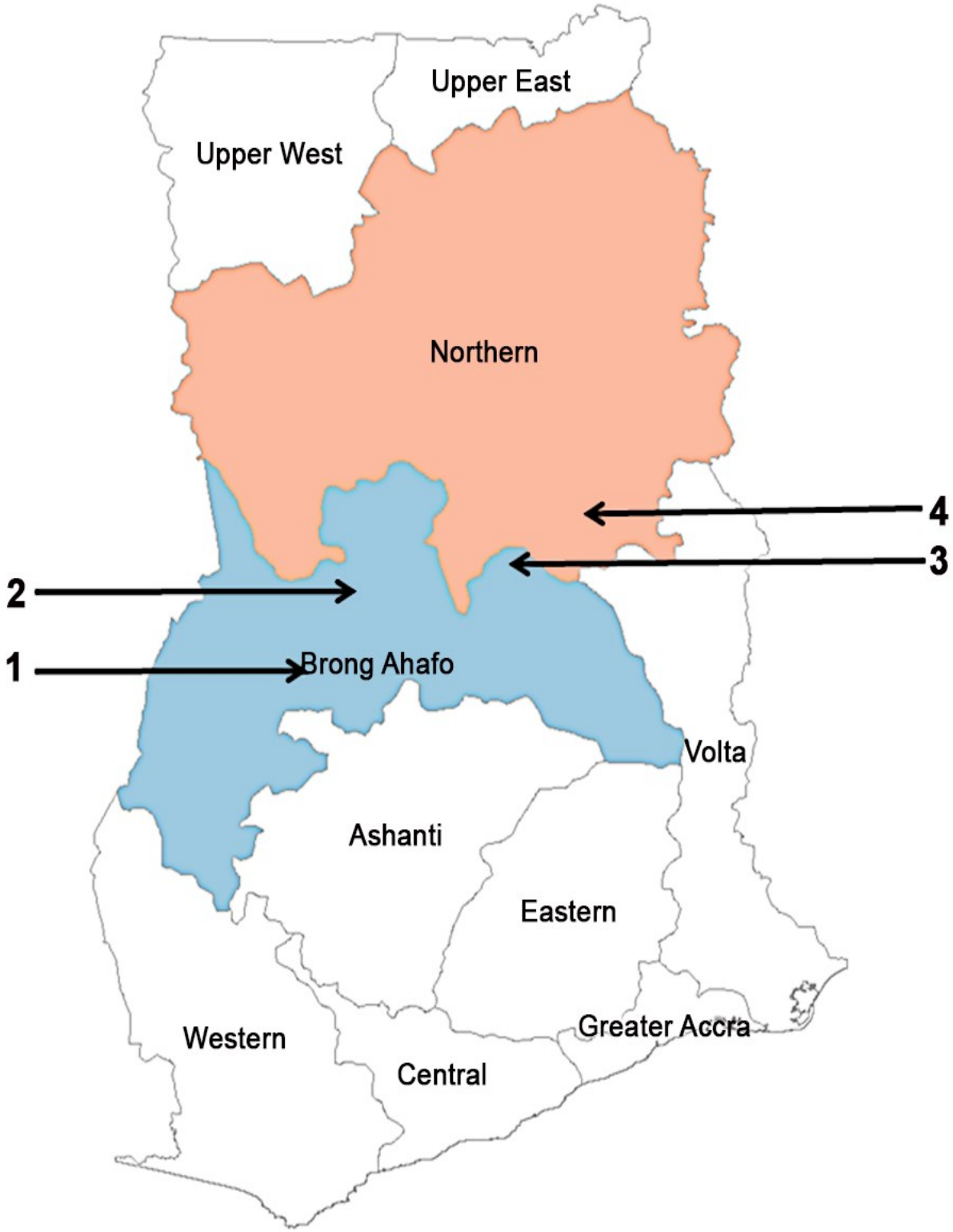

Figure 4.1. Map of Ghana indicating the sampled regions and districts. *The Brong-Ahafo and Northern regions are highlighted in light blue and light pink respectively. 1-Wenchi, 2-Kintampo North, 3-Pru, 4- Kpandai. Figure prepared by Mr Simon O'Hanlon (Imperial College London).*

Table 4.1. Description of ivermectin treatment in the areas where cost data were obtained in Ghana

Region	District	Treatment Frequency	Number of Persons Treated Per Year	Overall Therapeutic Coverage[§]	Total Population Size	Size (km^2)
Brong-Ahafo	Wenchi	Annual in all communities	27,881	90%	30,979	3,494
Brong-Ahafo	Kintampo North	Biannual in all communities	57,802	82%	70,490	5,108
Brong-Ahafo	Pru	Biannual in all communities	68,506	88%	77,848	2,195
Northern	Kpandai	Annual in 122 (55%) and biannual in 100 (45%) of 222 communities[†]	90,183	79%	114,156	1,772

[§] For the Wenchi and Kpandai districts, therapeutic coverage estimates were taken directly from national records pertaining to the last treatment round of 2010. For the Pru and Kintampo North districts, coverage estimates were derived from an average of two treatment rounds (the last round of 2010 and the first round of 2011). [†] A biannual strategy is used in 15 of 76 (20%) communities in the sampled sub-district, whereas the remainder 80% receive treatment annually. Therefore, the costs are likely to reflect more closely those of annual rather than biannual distribution.

Data were collected at various levels in the organization of the GHS. Firstly, information was gathered by conducting semi-structured interviews at the headquarters of the NTDP in Accra, and at the Regional Health Service directorates in the Brong-Ahafo region. Secondly, districts (and sub-districts where appropriate) were chosen to represent a range of geographical sizes, and population densities (Table 4.1). Thirdly, community drug distributors (CDDs) were interviewed in at least three communities in each district.

4.3.2. Perspective

In this study, the costs under investigation were those borne by the health care providers (such as the GHS, the major in-country partners, and the local communities). Therefore the cost of drug manufacture and transport to Ghana were excluded. Only data on the cost of

CDTI were collected; costs associated with individual, clinic-based treatment with ivermectin were ignored.

Data were collected on both the financial and economic costs of CDTI. Financial costs are those where a monetary transaction has taken place for the purchase of a resource. Economic costs also include, in addition to the financial costs described above, estimates of the monetary value of goods or services for which no financial transaction has taken place. Therefore, economic costs also account for the value of goods or services which could have been used for another purpose (opportunity costs). Examples of resources which have no financial costs but do have important economic costs are the 'free' use of building space provided by the Ghana Ministry of Health, the use of donated vehicles, and the time devoted to CDTI by unpaid CDDs. The costs associated with CDTI arise from various programmatic activities as outlined in Box 4.1.

Box 4.1. Programmatic Activities (partly based on (McFarland *et al.* 2005))

- **Drug Distribution Chain:** the process of getting the drugs from where they entered the country to the target population
- **Mobilization and Sensitization:** promotion, information dissemination and advocacy related to the project
- **Training of Volunteers:** training of community drug distributors (CDDs) (includes the costs incurred by both the trainers and the trainees)
- **Other Training:** all other training at whatever level (includes the costs incurred by both trainers and trainees)
- **Reporting:** the preparation and transmission of reports
- **Surveillance and Evaluation:** surveillance of the disease and treatment distribution at all levels
- **All Other Administration:** all other general office administration
- **Other Project Activities:** all other activities not already mentioned above

4.3.3. Data collection

Data collection was organized at the national, regional, district, sub-district and community levels and involved interviewing key personnel and scrutinizing national records. Data collected at the national level included records of funds provided by non-governmental organizations (NGO) such as Sightsavers, and others such as APOC (managed by the World Bank and implemented by the World Health Organization), among others. Given these multiple sources, it would have been most interesting to obtain a detailed breakdown of the relative contribution of each organization to the funding of onchocerciasis control in Ghana. Unfortunately, even at the national sampling level, it was rarely possible to separate the costs by their funding source. This, however, did not affect the study, which focused on the aggregate cost of onchocerciasis control. The costs collected were incurred in the year 2011. At each level, costs were collected according to different resource types (Box 4.2) using an approach based on methods described by McFarland *et al*. (2005) and the UNAIDS guidelines for costing studies (UNAIDS, 2000). First, the total gross expenditure on a resource (per year) was calculated from national records and/or questionnaires. Second, the most appropriate person(s) to answer questions on how the resource is used for activities relating to onchocerciasis control was selected for interview. Third, the interviewee was asked to indicate what fraction of time the resource was used for onchocerciasis control over the year (this was corroborated by multiple sources where possible). Multiplication of the total gross cost and fraction of time attributable to onchocerciasis control yielded an estimate of the recurrent yearly cost for a resource (such as an employee). The cost of capital resources (goods that last for more than one year, such as cars and computers) were estimated in a similar fashion, but the gross cost was spread over the average useful lifetime of the resource (a technique known as 'annualization') to arrive at an average yearly cost (UNAIDS, 2000). An annualization and discount rate of 3% was used to calculate the economic costs of capital resources (Johns *et al.* 2003). The average useful lifetime of all capital goods was assumed to be five years, in line with the value estimated by McFarland *et al*. (2005) and corroborated by study participants at the national level. However, the sensitivity of the results to this assumption was investigated by varying the average useful lifetime between 5 and 8 years (Nonvignon *et al.* 2012). The annual cost of building space was estimated as the

equivalent market rental value for the space being used for the control programme (UNAIDS, 2000).

The interviewee was also asked to estimate the fraction of time that the resource was used for itemized onchocerciasis control programmatic activities (Box 4.1). In addition, in districts receiving ivermectin biannually, the interviewees were asked to describe how their time spent on different CDTI activities had changed since increasing the treatment frequency to twice per year, and to indicate which of the CDTI activities are repeated for both treatment rounds.

Box 4.2. Resource Types (partly based on (McFarland *et al.* 2005))

- **Transportation (Capital Costs):** the capital costs associated with vehicles (e.g. the annualized[a] cost of motorbikes and cars)
- **Transportation (Recurrent Costs):** the recurrent costs associated with transport (e.g. fuel, insurance, maintenance, repairs, and rental costs)
- **Personnel:** the recurrent costs associated with paying salaries to employees (including any supplements or other benefits of employment)
- ***Per Diems*:** the recurrent costs associated with daily allowances (*per diems*)
- **Supplies and Equipment (Capital Costs):** other capital costs associated with a project, (e.g. annualized[a] costs of computers, photocopiers, and generators etc.)
- **Supplies and Equipment (Recurrent Costs):** the recurrent costs associated with project activities and general office running
- **Overheads:** the recurrent indirect costs associated with a project's specific utilities charges, building rental or equivalent
- **Volunteer Community Drug Distributor (CDD) Time:** the monetary value of the donated time of CDDs and other community members in implementing community directed treatment with ivermectin (CDTI)

[a] The annual share of the initial cost of capital equipment

At each level, and where relevant, interviewees were given the opportunity to express whether they had encountered any specific difficulties with the increasing of treatment frequency.

4.3.4. Data analysis

Costs collected at the national and regional levels, were factored down and costs from the sub-district and community levels factored up, with the aim of arriving at a value for the cost per person treated per year in each district (Figure 4.2). This is described for each of the levels below.

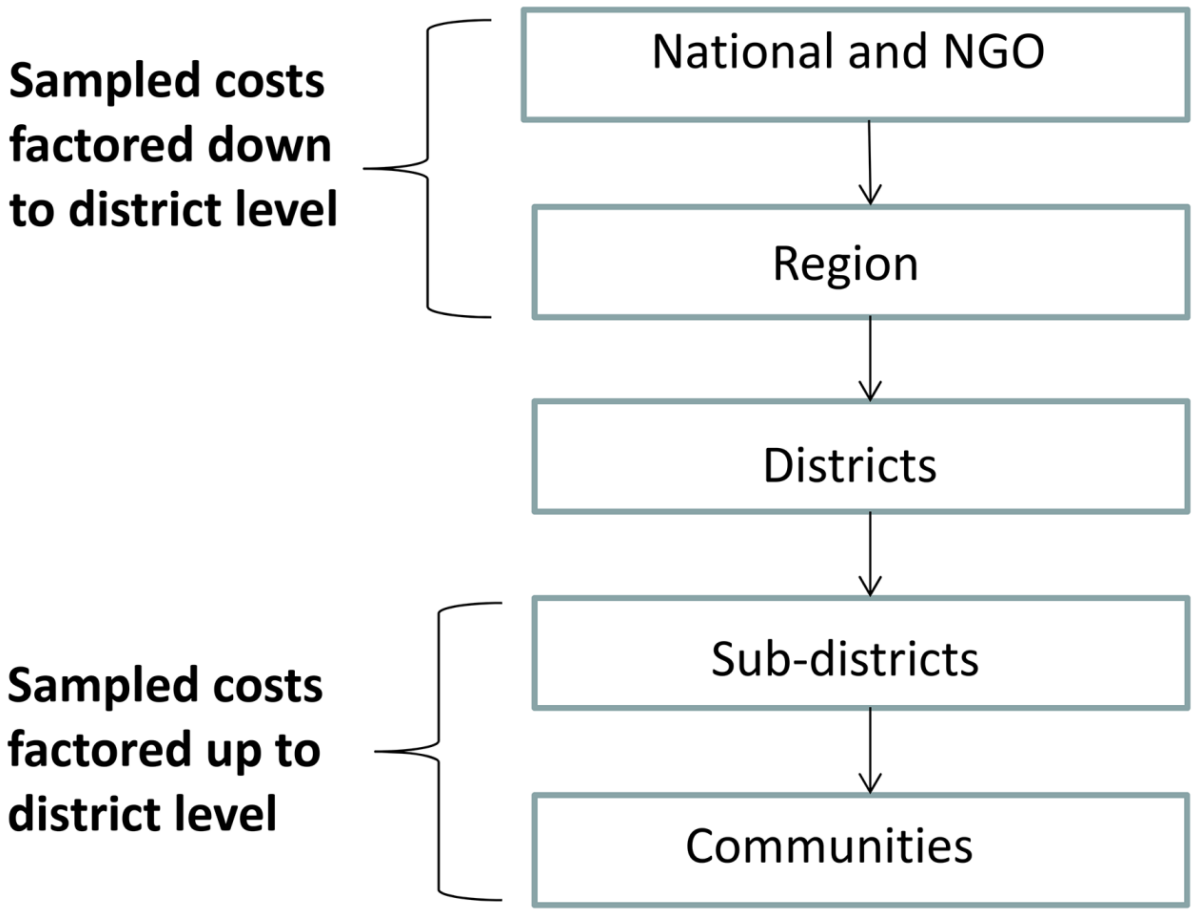

Figure 4.2. Organization levels at which data on cost of ivermectin distribution were collected.
NGO: Non-Governmental Organization.

National costs:

Of the 73 districts in Ghana where ivermectin is distributed, 40 (55%) are implementing biannual treatment. Consequently, when allocating the national costs to the districts, the costs were weighted according to the district's frequency of treatment. Based on responses to questionnaires, scrutinizing of national records, and conduction of semi-structured interviews, it was estimated that districts treating biannually were responsible for 70% of the total national cost. Separate costs (according to annual or biannual treatment) were allocated equally across districts receiving a certain treatment frequency. Based on interviews at the headquarters of the NTDP and the McFarland *et al.* (2005) study, it was assumed that the main drivers of the national costs were independent of target population size and therefore I did not adjust the national costs by the size of districts' target populations.

Regional costs:

These were distributed among districts using the same frequency of treatment-based weighting as used for the national costs. Due to logistic reasons on the terrain, it was only possible to estimate regional costs from one of the two regions from which districts were sampled. Thus, the costs incurred by the Northern region were assumed to be the same as those estimated from data pertaining to the Brong-Ahafo region.

Sub-district costs:

In each district included in this study one sub-district was sampled. The costs incurred by the sampled sub-districts were multiplied by the number of sub-districts within each district to aggregate the costs to the district level.

Community costs:

In each district included in this study three communities were sampled. In each sampled community, questionnaires were administered to the CDDs to ascertain to how many people they distributed ivermectin, and whether they received compensation from the district (this was corroborated at the local district health centres). Additionally, the opportunity cost of the volunteer CDDs' donated time was estimated by asking CDDs how much time they spent distributing the drug each treatment round. This donated time was converted to an equivalent number of 8-hour working days, which were valued according to the minimum wage in Ghana in 2011 (3.73 Ghana Cedis (GHC) per day (Wageindicator.org, 2012)). This figure

was reported to be equivalent to the daily wage of a hired farmland worker in the Brong-Ahafo region, the occupation of the majority of the interviewed distributors, and was subsequently used to estimate the value of the CDDs donated time across each district. However, to place a precise value on a CDD's donated time is difficult and whether or not it should be included is a matter of debate. Furthermore, the daily wage of a hired farmland worker can vary from district to district, and especially from region to region (Asante & Asenso-Okyere, 2003; Nonvignon *et al.* 2012). Therefore, the economic cost was calculated both including and excluding CDD's donated time, and the sensitivity of the results to the assumed daily wage was investigated (increasing or decreasing it by GHC1.00).

Currency conversion:
All costs were converted from the Ghanaian local currency (GHC), to United States dollars (US$), using the average 2011 exchange rate of US$1.00 to GHC1.58 (Exchange-rates.org, 2012). Reported costs from other studies were also converted to 2011 US dollars (using a consumer price index inflation calculator (United States Department of Labor, 2012)) to allow for valid comparison with these results.

4.4. Results

Table 4.2 shows the estimated financial and economic costs (including and excluding volunteer CDDs' time) of CDTI in the four sampled districts. The majority of the costs associated with CDTI were financial, with the extra economic cost per person per year (excluding CDDs' time) only adding US$0.01–US$0.03 (this includes the value of donated vehicles and use of free building space).

The estimated economic cost (excluding CDDs' time) of annual treatment in Wenchi district is US$0.40 per person per year. The economic costs (excluding CDD's time) of biannual treatment in the Pru and Kintampo North districts are approximately 50–60% higher (US$0.60 and US$0.64 per person per year respectively) than the corresponding annual costs. The estimated economic cost (excluding CDDs' time) for the Kpandai district (which uses a combination of an annual and biannual strategy –see Table 4.1 for description) is US$0.43 per person per year. These results were not sensitive to the assumed average useful lifetime of

capital goods; changing this from 5 to 8 years only changed the cost per treatment by a maximum of US$0.015.

Table 4.2. Financial and economic Costs (US$) per person treated per year in each district

Frequency of CDTI[§]	**Annual**	**Biannual**	**Biannual**	**Mixed**[†]
Cost type	**Wenchi**	**Kintampo North**	**Pru**	**Kpandai**
Financial cost	0.39	0.62	0.58	0.40
Economic cost (excluding volunteer CDD's[‡] time)	0.40	0.64	0.60	0.43
Economic cost* (including volunteer CDD's[‡] time)	0.45	0.73	0.69	0.50

[§] CDTI: Community-directed treatment with ivermectin. [†] Data from Kpandai district reflect a combination of annual (in 61 of 76 (80%) of the communities in the sampled sub-district) and biannual treatment frequency (see Table 4.1 and main text).[‡] CDD: Community Drug Distributor.* Economic costs include financial costs (monetary transactions) and estimates of the monetary value of goods or services for which no financial transaction has taken place (for example, the opportunity cost of the CDDs' time donated to administer ivermectin rather then working their fields) (UNAIDS, 2000).

4.4.1. Costs disaggregated by resource type and programmatic activity

Figure 4.3 depicts the cost of onchocerciasis control by CDTI disaggregated by resource type in the four sampled districts. The largest proportion of the total cost was associated with the payment of personnel. Recurrent transportation costs, such as the costs of fuel and vehicle maintenance, were the next most costly resource and showed the most variation among districts.

Figure 4.4 depicts the cost of CDTI-based onchocerciasis control disaggregated by programmatic activity in the four sampled districts. Surveillance and evaluation incurred the highest cost, followed by the drug distribution chain. For Pru and Kintampo North districts, the data show a noticeable increase in the reporting cost compared to Wenchi district.

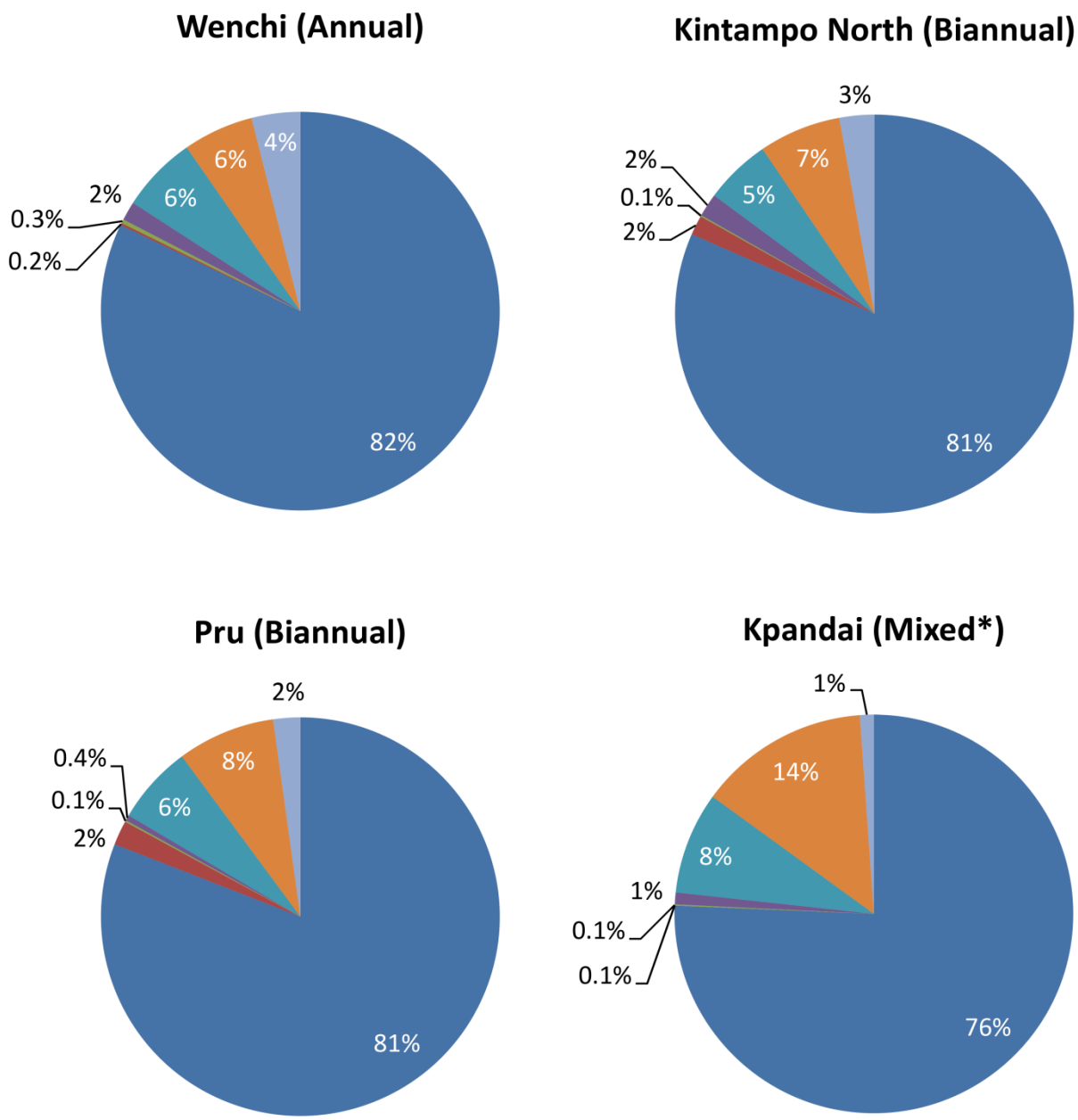

Figure 4.3. Economic costs at district, sub-district, and community levels disaggregated by resource type (excluding CDDs' time). *Personnel, Per Diems, Supplies and Equipment (Capital costs), Supplies and Equipment (Recurrent costs), Transportation (Capital costs), Transportation (Recurrent costs), Overheads. Definitions of different resource types are given in Box 4.2. *Data from Kpandai district reflect a combination of annual and biannual treatments.*

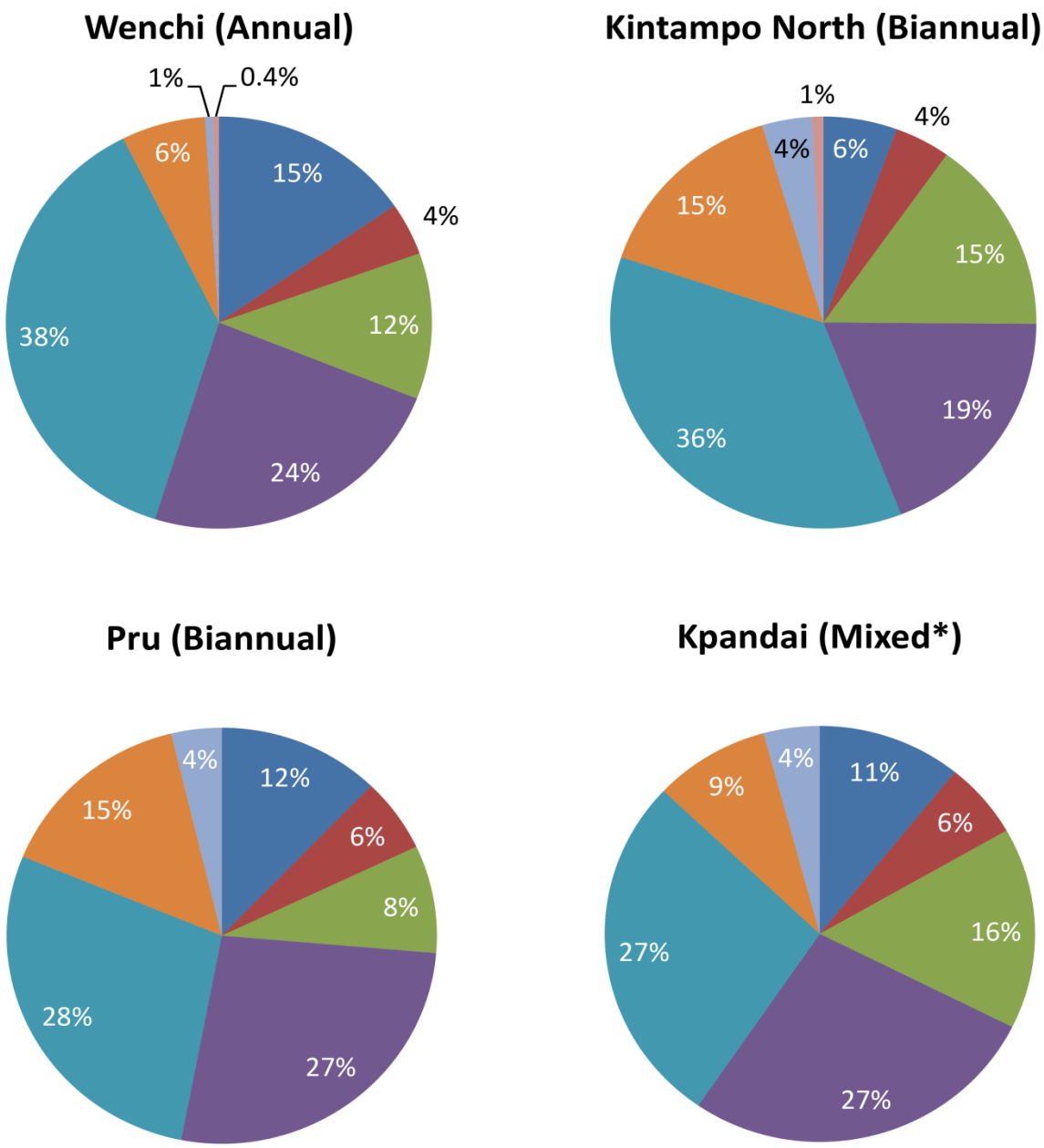

Figure 4.4. Economic costs at district, sub-district, and community levels disaggregated by programmatic activity (excluding CDDs' time). *Training of Volunteers, All Other Training, Mobilization/Sensitization, Drug Distribution Chain, Surveillance and Evaluation, Reporting, All Other Administration, Other Project Activities. Definitions of programmatic activities are given in Box 4.1. *Data from Kpandai district reflect a combination of annual and biannual treatments.*

4.4.2. Community distributors

From the pooled community data, it was estimated that there is one CDD for every 390 individuals and they spend an average of 61 hours distributing ivermectin each treatment round. The above value was used with data on the number treated in each district (Table 4.1) to estimate the total amount of time CDDs spend distributing the drug across the whole district. This increased the economic cost by US$0.046 per person per year when treating annually, and by US$0.092 when treating biannually (Table 4.2). This result was robust to the assumed daily wage of a hired farmland worker, which when increased or decreased by GHC1.00, only changed the economic cost of CDD per treatment by plus or minus US$0.012.

The CDDs reported receiving an average equivalent of US$3.17 in compensation for attending the distribution training sessions (which are conducted before each treatment round), and between US$3.17 and US$9.52 after distributing the drug. In this analysis, it was assumed that each distributor received the average (arithmetic mean) of the reported values (a total of US$9.96 in compensation for both training and distribution for each treatment round).

4.4.3. Reported difficulties

The implementation of a large-scale, mass biannual ivermectin treatment strategy was reported at the district and sub-district level as being well received and perceived as sustainable in the future. However, the disease control officers at the district health centres in the sampled districts in which biannual treatment is being implemented, reported that increasing the treatment frequency to twice per year substantially increased the workload by increasing the amount of time they spent on reporting activities (the percentage of the economic cost at the district, sub-district, and community levels attributed to reporting activities increased from 6% in the districts (Wenchi) treated annually to 15% in the districts treated biannually (Pru and Kintampo North) (Figure 4.4)).

4.5. Discussion

The estimated economic cost of annual CDTI in Wenchi district, i.e. US$0.40 per person per year excluding CDDs' time, is consistent with the lower range of costs reported by

McFarland *et al*. (2005), who estimated an average economic cost (excluding CDDs' time) of US$0.62 (2011 prices) per person per year from 10 regions (excluding one region co-endemic with *Loa loa*) across Cameroon, Nigeria and Uganda (with values ranging from US$0.39 to US$2.77 (2011 prices)). The estimated cost of annual CDTI presented here is 1.4 times higher than the US$0.29 (2011 prices) per person estimated by Onwujekwe *et al*. (2002) using data from two Nigerian communities. However, the Nigerian study used a smaller sample of only two communities, and did not collect costs from as an extensive range of sources as this study, or as done by McFarland *et al*. (2005). Katabarwa *et al*. (2002) estimated that in districts of a similar population size to Wenchi, the cost per treatment was US$0.34 (2011 prices). However, in districts with a larger population (> 100,000 inhabitants) the cost fell substantially to US$0.13 (2011 prices). These estimates are broadly consistent with the cost of annual mass drug administration (MDA) for lymphatic filariasis control presented by Goldman *et al.* (2007), in which the estimated financial cost per treatment (with donated ivermectin and albendazole) in Ghana was US$0.21 (2011 prices) but varied between US$0.08 and US$2.91 (2011 prices) across the whole multi-country study.

The estimated cost of biannual CDTI per person per year in the Pru and Kintampo North districts was 50–60% higher than the estimated cost of annual (in Wenchi) treatment. This is consistent with the estimated increase in costs associated with biannual MDA for lymphatic filariasis control provided by Stolk *et al.* (2013) (who estimated for Africa, a 63% increase in the cost of treatment per year excluding the value of donated drugs). These costs are higher than estimates for biannual treatment at smaller scales and specific age groups, such as in school-based anthelmintic treatment programmes. For instance, Phommasack *et al*. (2008) found that the annual cost of treatment of soil-transmitted helminthiases in a school-based programme was 35% higher in provinces treating biannually than in those treating annually. However, school-based treatment programmes are implemented differently than community-based programmes and therefore the change in costs of different treatment frequencies cannot be directly compared.

Caution is also advised when comparing the costs of different strategies estimated using data from different districts. This is because districts have different characteristics, such as road conditions, spread of communities, and population densities, which will affect the estimated cost of CDTI. Because of these potential difficulties, study participants in the Pru and

Kintampo North districts were asked to estimate (based on their previous experience) the percentage allocated to a given resource had this resource hypothetically been used for an annual treatment strategy. Thus, the estimated hypothetical economic cost (Table 4.3) of treating annually in the Pru and Kintampo North districts (US$0.39 and US$0.43 per person per year, respectively) were consistent with the actual cost estimates of treating annually obtained for Wenchi (US$0.40 per person per year). This supports the estimated 50–60% increase in costs when treating biannually compared to treating annually. The difficulties associated with comparing fairly costs among districts within Ghana exemplify a more general conundrum of comparing results of health economic analyses conducted in different locations, such as the complexity of comparing data collected from different countries with differently structured economies and healthcare systems, and where public health interventions may comprise different (e.g. school-based versus community-based) modalities of delivery.

Table 4.3. Hypothetical cost (US$) of annual CDTI in Kintampo North and Pru districts, Brong-Ahafo region, Ghana

Cost Type	Estimated Annual Cost Per Person Treated if Annual Distribution were Implemented	
	Kintampo North	**Pru**
Financial cost	0.42	0.38
Economic cost (excluding volunteer CDD's time)	0.43	0.39
Economic Cost (including volunteer CDD's time)	0.47	0.44

The estimated economic cost of CDTI in the Kpandai district, where both annual and biannual treatments are delivered, likely reflects more closely the cost of annual rather than biannual CDTI since only 15 of 76 (20%) of the communities in the sampled sub-district receive biannual treatment (with the remaining 80% receiving annual CDTI). This possibly explains why the estimated cost per person per year in the Kpandai district was only

marginally higher than that in Wenchi (US$0.43 for the former versus US$0.40 for the latter), in which only annual treatments are delivered. Furthermore, Kpandai has a very high population density which could reduce the cost per treatment (as found in Katabarwa *et al.* (2002)). Across the whole district, 122 of 222 (55%) of the communities are treated annually and the remaining 45% receive biannual CDTI. Therefore, it is reasonable to expect overall, the actual cost of ivermectin treatment for Kpandai will lie in between the estimated costs of annual and biannual CDTI.

4.5.1. Costs disaggregated by resource type and programmatic activity

The costs disaggregated by resource type were consistent among the sampled districts. These data are also similar to those presented by McFarland *et al*. (2005). The recurrent transportation cost was notably higher in Kpandai compared with the other districts. This may in part be due to the poorer quality of roads in the area, resulting in higher vehicle maintenance and fuel costs (although many other factors, including the spread of the communities, also affect transportation costs). The costs disaggregated by programmatic activity showed slightly more variation among districts than among the different resource types. It is noteworthy that in the Pru and Kintampo North districts (and to a lesser extent in the Kpandai district), the percentage of the economic cost attributed to reporting activities at the district, sub-district, and community levels is substantially higher than that in the Wenchi district (15% in Pru and Kintampo North compared to 6% in Wenchi) (Figure 4.4). This was attributed to the increase in treatment frequency and is discussed in further detail in section 4.5.3.

4.5.2. Community distributors

The compensation system for CDDs has recently been implemented in Ghana to cover their transport costs, to facilitate attendance of training days, and to help serve as an added incentive. The amount received by CDDs per treatment round was corroborated at the district health centres. Generally, the reported amount received by the community distributors was very consistent across communities and districts.

Accounting for the volunteer CDDs' time added approximately US$0.05 per person per treatment round. The is consistent with the value reported by Onwujekwe *et al*. (2002), who

found that taking into account volunteer CDD time in two Nigerian communities added approximately US$0.07 (2011 prices) per person per treatment round (using the Nigerian minimum wage to value the volunteer CDDs' time). However, both the estimates presented here and the those of Onwujekwe *et al.* (2002) are substantially lower than that reported by McFarland *et al*. (2005), who estimated that accounting for volunteer CDDs' time added an average of US$0.19 (2011 prices) per treatment round (valuing volunteer time based on the average per capita Gross National Income (GNI) for each of the three countries studied in McFarland *et al*. (2005), namely, Cameroon, Nigeria and Uganda). However, this estimate was highly variable between the different study sites (US$0.05–0.54 (2011 prices) per treatment round). The use of different methods to value donated CDDs' time (see below) could partly explain the difference (i.e. estimation using the country's minimum wage, or using the country's per capita GNI). Other possible explanations include the occurrence of cultural differences affecting the time it takes to distribute the drug.

As mentioned above, the method used to value the volunteer CDD's time has marked effects on the cost output. For example, it was assumed the market value of the volunteer CDD's time to be US$2.36 per day (the minimum wage in Ghana of GHC3.73 divided by the 1.58 exchange rate (Exchange-rates.org, 2012)) based on the wage that a farmland worker would receive (i.e. the wage received for the most common alternative occupation) (Wageindicator.org, 2012; World Bank, 2013)). However, had the volunteer CDDs' time been valued using the per capita GNI method (as used by McFarland *et al.* (2005)), this figure would have increased to US$4.96 per day (Wageindicator.org, 2012; World Bank, 2013). This difference may seem relatively small but when these costs are factored up to the district level, they can become substantial.

4.5.3. Reported obstacles associated with switching from annual to biannual CDTI

Disease control officers at the district health centres reported that increasing the treatment frequency to twice per year increased substantially the amount of time they spent on reporting activities. This is consistent with the costs disaggregated by programmatic activity (Figure 4.4), which indicate that the time spent on reporting activities increased more than any other project activity when comparing biannual and annual treatments. This may potentially lead to

delays in ivermectin being delivered to the districts, if the necessary reports for the next dispatch of drugs are not completed on time (delivery of the next batch of ivermectin being contingent on reporting). Delays in the delivery of treatment to communities not only will have administrative implications, but more importantly, transmission implications. Treating individuals every 6 months is highly important for transmission suppression, as it has been estimated that adult *Onchocerca volvulus* female worms start recovering from the temporary sterilising (embryostatic) effects of ivermectin approximately between three and four months after treatment, and by six months microfilarial production has recuperated to a substantial degree (Basáñez *et al.* 2008). Therefore, delays in treatment will permit more transmission, ultimately making the disease harder to eliminate and diminishing the benefit of treating biannually. National onchocerciasis control programmes which consider increasing CDTI frequency may need to support reporting activities at the district level and potentially at the drug donation programme level to encourage timely reporting but also to allow greater flexibility in deadlines to minimize delays in drug distribution.

4.6. Conclusions

The estimate of the cost of annual CDTI is consistent with the range of values previously reported in the literature (Katabarwa *et al.* 2002; McFarland *et al.* 2005; Onwujekwe *et al.* 2002). The results indicate that the cost of biannual ivermectin treatment was approximately 50–60% higher than the cost of annual treatment, and that simply doubling the cost of annual CDTI does not yield a correct estimate as some studies have assumed (Ndyomugyenyi *et al.* 2007). This is higher than estimates for increasing treatment frequency obtained at smaller scales and when targeting specific age groups, such as those associated with school-based anthelmintic treatment programmes (Phommasack *et al.* 2008), which are not truly relevant for onchocerciasis, but similar to estimates for the more comparable lymphatic filariasis control programme (Stolk *et al.* 2013). This study will be beneficial in informing economic evaluations regarding cost-effectiveness analyses of increasing CDTI frequency from annual to biannual in the African context for the control and elimination of human onchocerciasis.

4.7. Limitations

In Ghana, onchocerciasis control is under the remit of the NTDP and therefore different disease control programmes are often integrated. For example, onchocerciasis and lymphatic filariasis control activities are often carried out simultaneously. Potentially, this can lead to difficulties in obtaining accurate costs for a single disease intervention. In addition, this study was retrospective, and therefore, to a certain extent, the data obtained were subject to some degree of recall bias.

In order to reduce the time and logistical complexity involved in collecting the cost data, the sampling strategy was not random, as we purposely visited local government offices and communities in districts where CDTI was annual, biannual, or a combination of the two. Furthermore, it was only possible to obtain data in one district that implements annual treatment and one sub-district in each of the districts. Also, the selected districts may have been more accessible by road from Accra, the capital of Ghana, than other more remote locations. Nonetheless, there is no reason to assume that the costs reported for the sites included in this study (either delivering annual or biannual CDTI) are not representative of other sub-districts in the area, nor is there a treatment cost-associated reason as to why an area switched from annual to biannual CDTI other than the parasitological criteria listed above. This is confirmed by the similarity of cost estimation of annual treatment between the districts delivering only annual CDTI and the sub-districts also delivering yearly treatment within districts implementing both strategies. Due to logistic reasons, the regional level costs in the Northern region were assumed to be the same as those estimated from Brong-Ahafo region. However, due to differences between the regions (such as road networks and community scattering), the costs incurred in the Northern region may be higher. Nevertheless, this assumption will not affect the main conclusions of the study regarding the relative costs of annual vs. biannual treatment.

Chapter 5: An Economic Evaluation of Increasing the Frequency of Ivermectin Treatment in Africa

5.1 Summary

In this chapter the health impact, programmatic cost, and projected duration of biannual vs. annual ivermectin treatment is evaluated in a range of endemic, economic and programmatic scenarios typical of savannah onchocerciasis foci in Africa. The findings indicate that though biannual treatment yields only small additional health benefits (in terms of DALYs averted) over those of annual treatment, its benefit is pronounced in the context of elimination goals, shortening timeframes to reach the proposed operational thresholds for stopping treatment. Additionally, these projected reductions in programme duration were found to potentially lead to programmatic cost savings. Furthermore, the results indicate that switching to a biannual treatment strategy reduces the heterogeneity in the projected timeframe for elimination among settings with a different pre-control endemicity, and consequently may substantially reduce cross transmission among contiguous onchocerciasis foci and infection re-introduction into controlled areas. However, notwithstanding these conclusions, the feasibility of increasing from one to two treatments yearly will vary with the specific programmatic circumstances.

A modified version of this chapter is currently under review: Turner, H.C., Walker, M., Churcher, T.S., Osei-Atweneboana, M.Y., Biritwum, N-K., Hopkins, A., Prichard, R.K. and Basáñez, M-G. Reaching the London Declaration on Negected Tropical Diseases for onchocerciasis: an economic evaluation of increasing the frequency of ivermectin treatment in Africa

5.2. Introduction

The predominant onchocerciasis control strategy in Africa is annual mass drug administration (MDA) with ivermectin. Recently, there has been a shift in onchocerciasis control policy in Africa, with the aim of programmes' changing from morbidity control to elimination of infection (Section 1.9). In this context, switching to biannual (twice per year) treatment in Africa might improve chances of elimination (Gustavsen *et al.* 2011; Ndyomugyenyi *et al.* 2007), a strategy partly motivated by its success in onchocerciasis foci in Latin America (Gustavsen *et al.* 2011) (Gonzalez *et al.* 2009; Rodriguez-Perez *et al.* 2010). Some African countries, such as Ghana and Uganda, have already adopted large-scale biannual treatments in selected foci (Ndyomugyenyi *et al.* 2007; Osei-Atweneboana *et al.* 2007). However, the likely impact of this strategy more generally in Africa, and how it can help achieve the goals set by the World Health Organization (WHO) and London Declaration on Neglected Tropical Diseases (LDNTD) (World Health Organization, 2013), has not been investigated.

In this chapter, by linking a transmission dynamics model (Chapter 2), disease model (Chapter 3) and cost data (Chapter 4), the health impact, programmatic cost and projected duration, of biannual versus annual ivermectin treatment is evaluated evaluate in a range of endemic, economic and programmatic scenarios typical of savannah onchocerciasis foci in Africa.

5.3. Method

5.3.1. Operational thresholds for treatment interruption followed by surveillance (OTTIS)

Based on experiences in foci in Mali and Senegal (Diawara *et al.* 2009; Tekle *et al.* 2012), cessation of onchocerciasis control in the OCP and ONCHOSIM projections, APOC has set operational thresholds for treatment interruption followed by Surveillance (OTTIS). Namely, these are a microfilarial prevalence (by skin snipping) <5% in all surveyed villages and <1% in 90% of such villages, and <0.5 infective larvae per 1,000 flies (African Programme for Onchocerciasis Control, 2010). Based on these thresholds, it was assumed that when the modelled microfilarial prevalence (all ages) fell to <1.4% (the weighted mean (arithmetic) of

the two prevalence thresholds above), measured just before the next treatment round, the OTTIS would have been achieved, determining MDA programme duration. It is important to realise that the OTTIS values are not truly a transmission breakpoint (parasite density below which the worm population would not be able to maintain itself (Basáñez *et al.* 2009; Duerr *et al.* 2011; Gambhir *et al.* 2009)), but rather programmatic goals indicating the cessation of MDA and the commencement of post-MDA surveillance. As OTTIS values are provisional, they are varied in the sensitivity analysis (Table 5.1).

5.3.2. Health impact

The number of disability-adjusted life years (DALYs) averted were used to quantify the health impact of ivermectin, combining into a single metric the burden of onchocercal disease resulting from blindness, visual impairment, troublesome itching and premature death (see Chapter 3 for a description of the disease model). DALYs are particularly useful for policy makers and healthcare providers, because they are a more comprehensive measure of population health than mortality estimates, allowing comparisons among a wide range of health interventions (Disease Control Priorities Project, 2006).

5.3.3. Costs of mass drug administration

Based on costing data collected in savannah foci in Ghana (Chapter 4), it was estimated that the economic cost of annual community-directed treatment with ivermectin (CDTI) is US$41,536 per target population of 100,000 individuals (overall population) per year (2012 prices) and that this would increase by 60% when treating biannually (Chapter 4). (This cost of annual CDTI was derived from the cost per treatment and population size of the Wenchi district, presented in Tables 4.1 and 4.2 (inflated to 2012 US$ (United States Department of Labor, 2012))). However, due to uncertainty in generalising this estimated cost increase to other African countries, this was varied in the sensitivity analysis (Table 5.1). Costs were collected from the health care providers' perspective, i.e., national control programmes of endemic countries, non-government organization (NGO) partners, and volunteer community distributors (CDD) (Chapter 4). However, as part of the sensitivity analysis the additional economic value of donated ivermectin tablets was also included, assuming a commercial, per tablet, price of US$1.50 plus US$0.005 shipping costs, and that an average treatment requires 2.8 tablets per person (Coffeng *et al.* 2013).

5.3.4 Model outcomes and sensitivity analysis

The model was used to compare the impact of annual versus biannual CDTI over a 50-year time horizon in terms of the projected health impact (DALYs averted), programme cost and duration. This long-time horizon was used in order to compare adequately the two strategies in the context of 2020/2025 elimination goals; MDA programmes have been on-going in many areas since the mid 1990's (and in some since 1988) – see section 1.5. Three pre-control endemicity levels, namely, 40%, 60% and 80% pre-control microfilarial prevalence, were investigated to represent a range from mesoendemic to highly hyperendemic areas (Table 1.1). A summary of the pre-control conditions for the three endemicity levels investigated is shown in Table 3.1. Changing to a biannual treatment strategy at different stages of an ongoing annual MDA programme was also investigated; switching to twice-yearly CDTI at microfilarial prevalence values of 30%, 20% and 15%, motivated by programmatic assessments conducted in Ghana before switching to biannual treatment in 2009 (Chapter 4). In line with WHO guidelines (World Health Organization, 2003), a discount rate of 3% was applied to both the health benefits and the costs, and this rate was varied in the sensitivity analysis.

Table 5.1 summarises the parameter definitions and values that were explored in the sensitivity analysis.

Table 5.1. Summary of parameter definitions and values explored in the sensitivity analysis

Parameters	Values
Overall proportion of the total population receiving ivermectin at each round, referred to as therapeutic coverage	60-80%
Proportion of the eligible population who never take treatment, referred to as the proportion of systematic non-compliers	0.1-5%
Increase in cost (per year) of biannual compared to annual community-directed treatment with ivermectin (CDTI)	40-80%
Discount rate applied to the health benefits and costs	0-6%
Inclusion of the economic value of the donated ivermectin tablets	See 5.3.3. *Cost of mass drug administration*
The per dose reduction in microfilarial production of female adult worms, referred to as the anti-macrofilarial action of ivermectin	7-30%
Operational thresholds for treatment interruption followed by surveillance (OTTIS)	1.4±0.5% microfilarial prevalence

5.4. Results

Model outputs indicate that annual CDTI is highly cost-effective (Table 5.2 and Figure 5.1). The health impact, cost-effectiveness, and projected MDA duration, were strongly related to pre-control endemicity levels; the higher the pre-control microfilarial prevalence, the greater the health impact and cost-effectiveness but the longer the projected programme duration (Table 5.2 and Figure 5.2).

Table 5.2. Cost-effectiveness of annual and biannual ivermectin treatment programmes for onchocerciasis control at different levels of pre-control endemicity

Pre-control endemicity (microfilarial prevalence)	Ratio of total health impact (biannual/annual)	Ratio of total cost (biannual/annual)	Cost-effectiveness ratio of annual ivermectin treatment (US$) [†]	Incremental cost-effectiveness ratio of biannual ivermectin treatment (US$) [§]
Mesoendemic (40%)	1.03	1.13	11**	48*
Hyperendemic (60%)	1.03	1.16	5**	31**
Highly hyperendemic (80%)	1.03	1.12	3**	12**

[†] The ratio of the total cost and the total number of DALYs averted (i.e. the cost per DALY averted) of an annual ivermectin treatment programme. [§] The ratio of the incremental cost and the incremental number of DALYs averted by a biannual compared to annual ivermectin treatment programme (i.e. the extra cost per extra health gain). **Highly cost-effective (< US$40 per DALY averted), *cost-effective (US$40 to US$238 per DALY averted) based on the World Bank cost-effectiveness thresholds (inflated to their 2012 equivalent) (World Bank, 1993). The analysis was performed with a 50-year time horizon, discount rate of 3% applied both to costs and health benefits, therapeutic coverage of 80%, 0.1% systematic non-compliers, perennial transmission, and 7% cumulative reduction in microfilarial production by female adult worms per ivermectin dose. Costs do not include those incurred by Merck & Co. A summary of the pre-control conditions is provided in Table 3.1.

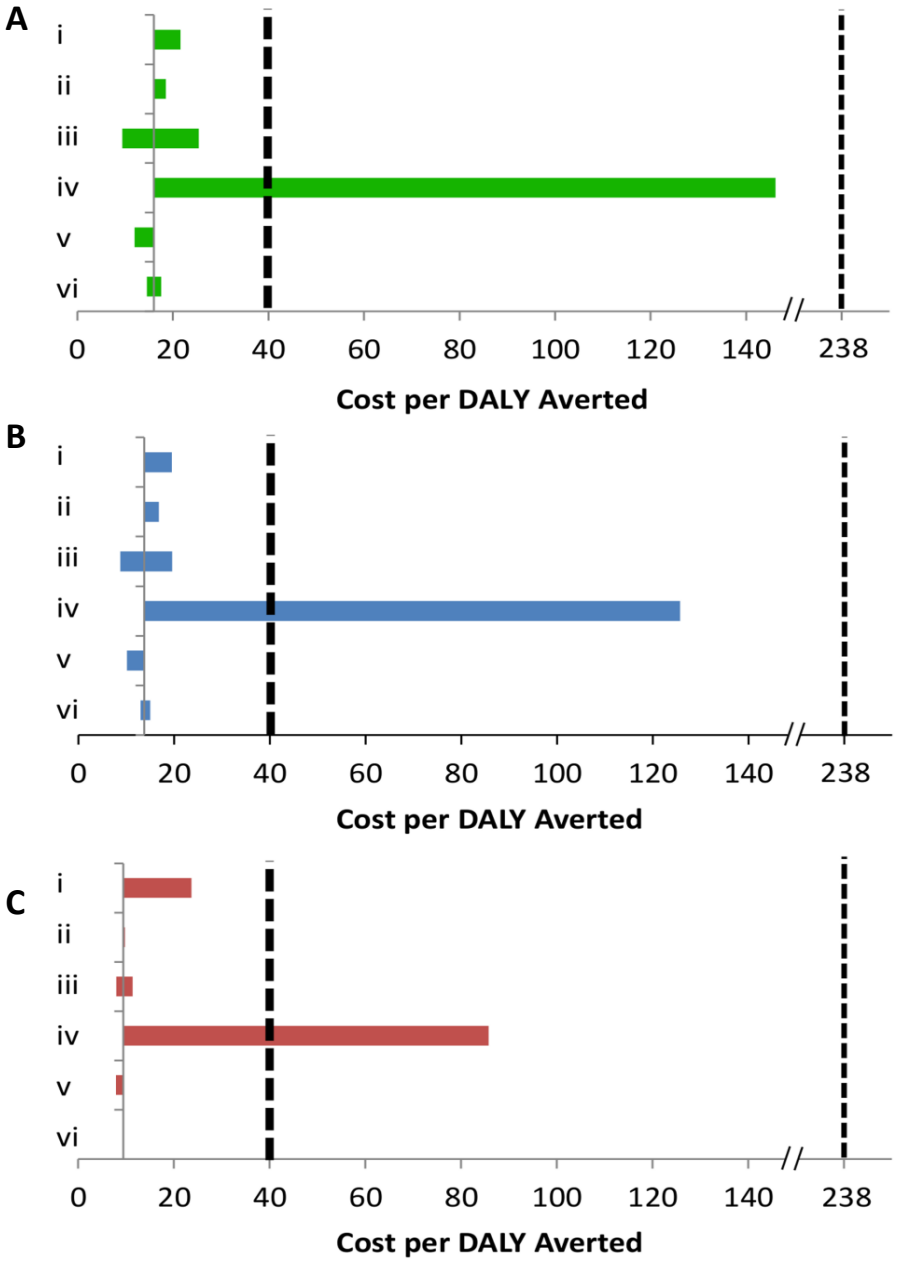

Figure 5.1. Univariate sensitivity analysis of the cost-effectiveness of an annual ivermectin treatment programme for onchocerciasis control. *Panels **A**, **B**, and **C** correspond to, respectively, a pre-control endemicity of 40%, 60%, and 80% microfilarial prevalence. The baseline cost-effectiveness (with the assumptions outlined in the legend of Table 5.2) is indicated by the thin grey horizontal line. i: Decrease in therapeutic coverage from 80% to 60%. ii: Increase in the proportion of systematic non-compliance from 0.1% to 5%. iii: Change in the discount rate from 3% ± 3% (i.e. 0-6%). iv: Inclusion of the value of the donated ivermectin tablets. v: Higher anti-macrofilarial action of ivermectin (i.e. a 30% instead of a 7% per dose reduction in microfilarial production of exposed female adult worms). vi: Different operational thresholds for treatment interruption (1.4 ± 0.5%). Thick and thin dashed lines represent the thresholds for the intervention being highly cost-effective <US$40 per DALY averted), and cost-effective (<US$238 per DALY averted), based on World Bank criteria of cost per DALY averted (inflated to their 2012 equivalent).*

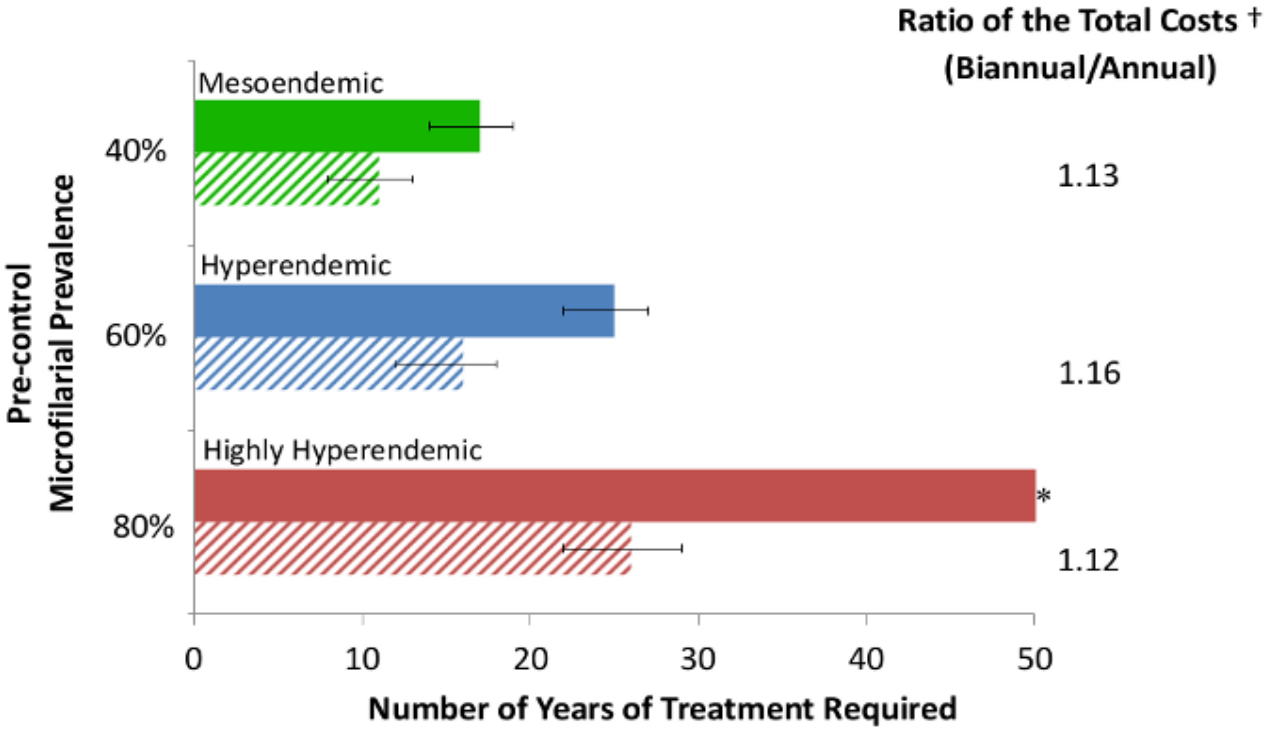

Figure 5.2. Comparison of annual vs. biannual ivermectin treatment in areas where onchocerciasis control has not been previously implemented. *Annual and biannual ivermectin treatments are indicated by solid and dashed bars respectively. Error bars represent varying the operational thresholds for treatment interruption (1.4% microfilarial prevalence) by ± 0.5%. The analysis was performed with a 50-year time horizon, discount rate of 3% applied both to costs and health benefits, therapeutic coverage of 80%, 0.1% of systematic non-compliers, perennial transmission, and a 7% cumulative reduction in microfilarial production by female adult worms per ivermectin dose. A summary of the pre-control conditions is provided in Table 3.1. *Operational threshold for treatment interruption not attained within the 50 year time horizon. † Costs do not include those incurred by Merck & Co.*

The projected incremental health gain of biannual versus annual CDTI (i.e. the additional number of DALYs averted) was small, with biannual treatment not being more cost-effective than annual treatment (Table 5.2). However, biannual treatment notably shortened the projected duration of MDA. Additionally, switching from an annual to a biannual treatment strategy during an ongoing MDA programme can also reduce programme duration, particularly in highly hyperendemic areas (where annual CDTI would not suffice to reach OTTIS), potentially generating programmatic cost savings (Figure 5.3). Though, in mesoendemic foci the reduction in programme duration was less pronounced. Furthermore, the heterogeneity in the projected programme duration among areas of different pre-control endemicity is substantially reduced when using a biannual treatment strategy (Figure 5.3).

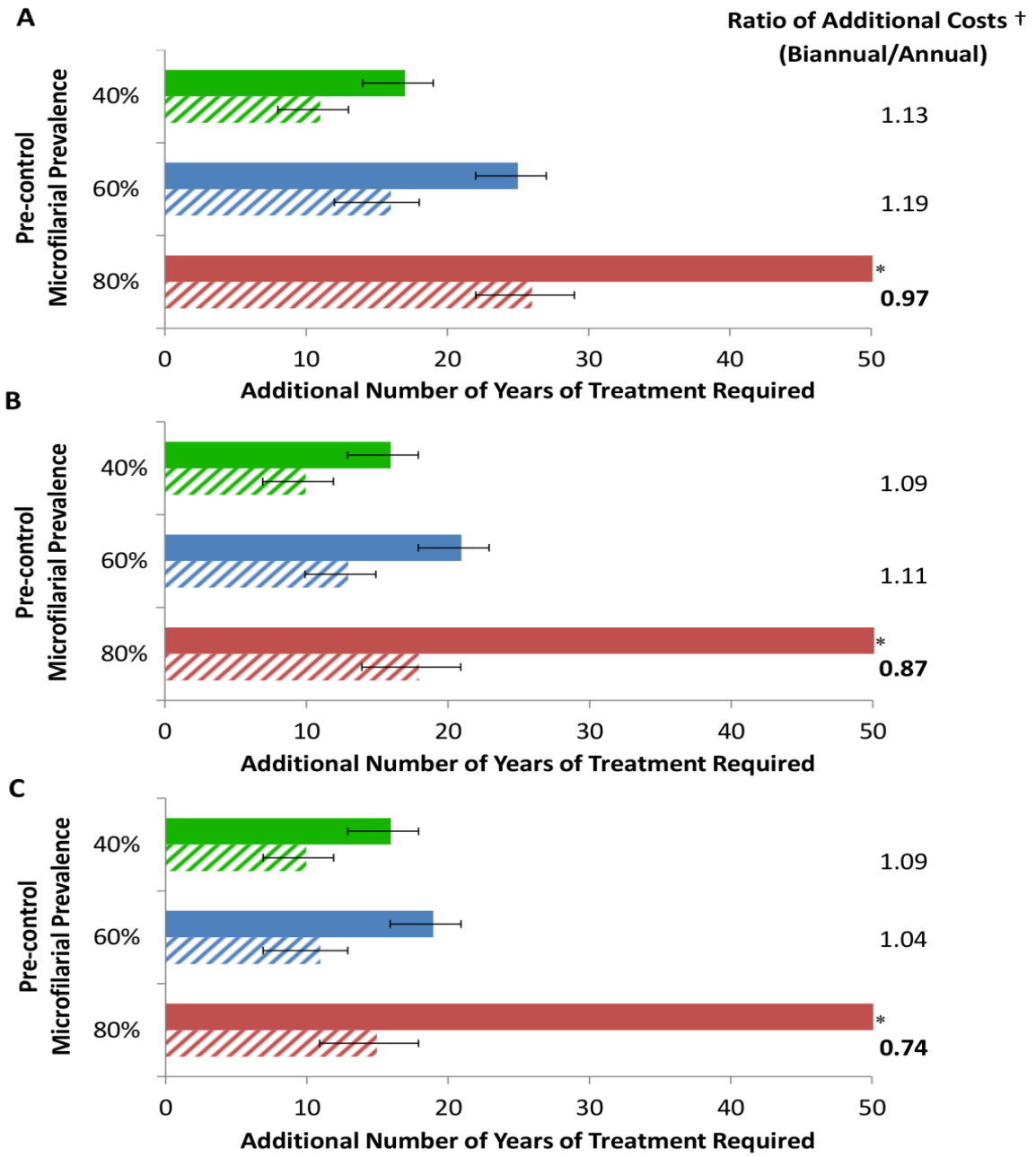

Figure 5.3. Impact of switching to biannual ivermectin treatment at different stages of an ongoing annual onchocerciasis treatment programme. *Panels **A**, **B**, and **C** correspond to, respectively, switching from annual to biannual treatment at 30%, 20%, and 15% microfilarial prevalence. The green, blue and red lines correspond to, respectively, a pre-control endemicity of 40%, 60%, and 80% microfilarial prevalence. Annual and biannual ivermectin treatments are indicted by solid and dashed bars respectively. Error bars represent varying the operational thresholds for treatment interruption by ± 0.5%. The number of additional years of treatment and the ratio of additional costs are considered from the point of the switch to biannual treatment (as opposed to the start of control). The microfilarial prevalence at the time of the switch was assumed to be measured just before the next round of treatment is distributed. Modelling assumptions are as in the legend of Figure 5.2.* Operational threshold for treatment interruption not attained within the 50 year time horizon. † Costs do not include those incurred by Merck & Co.*

5.4.1 Sensitivity analysis

Therapeutic Coverage and Compliance:

Varying the levels of therapeutic coverage and systematic non-compliance (Table 5.1) did not affect substantially the projected health impact of annual or biannual CDTI (Table 5.3). However, if the therapeutic coverage is low, there is a slightly greater incremental health gain when treating biannually (Table 5.4). Varying coverage and compliance markedly influenced the projected programme duration and total cost of MDA; therapeutic coverage exerted a more pronounced effect (which increased with increasing pre-control endemicity) on annual CDTI, while systematic non-compliance had a pronounced effect on biannual CDTI (Tables 5.3-5.4 and Figure 5.4).

Table 5.3. Sensitivity of health impact, total cost and duration of annual and biannual ivermectin treatment programmes for onchocerciasis control to different levels of coverage and systematic non-compliance

Pre-control endemicity	Percentage change in health impact		Percentage change in total cost		Percentage change in programme duration	
	Annual	Biannual	Annual	Biannual	Annual	Biannual
Effect of assuming 60% versus 80% overall therapeutic coverage						
Mesoendemic	-5%	-1%	24%	15%	35%	27%
Hyperendemic	-4%	-1%	27%	14%	48%	19%
Highly hyperendemic	-3%	-1%	NA	25%	NA	46%
Effect of assuming 5% versus 0.1% systematic non-compliance						
Mesoendemic	-2%	-2%	13%	35%	18%	45%
Hyperendemic	-2%	-3%	17%	34%	28%	50%
Highly hyperendemic	-3%	-4%	NA	43%	NA	285%

NA: Operational thresholds for treatment interruption not attained within the 50-year time horizon. Pre-control microfilarial prevalence and modelling assumptions are as in the legend of Table 5.2.

Table 5.4. Sensitivity of the relative health impact and total cost of biannual compared to annual ivermectin treatment programmes for onchocerciasis control to different levels of coverage and systematic non-compliance

Pre-control endemicity	Systematic non-compliance	80% overall therapeutic coverage		60% overall therapeutic coverage	
		Ratio of total health impact (biannual/annual)	Ratio of total cost (biannual/annual)	Ratio of total health impact (biannual/annual)	Ratio of total cost (biannual/annual)
Mesoendemic	0.1%	1.03	1.13	1.07	1.11
	5.0%	1.03	1.35	1.07	1.24
Hyperendemic	0.1%	1.03	1.16	1.07	1.04
	5.0%	1.02	1.33	1.06	1.19
Highly hyperendemic	0.1%	1.03	1.12	1.07	1.40
	5.0%	1.02	1.60	1.05	1.60

Pre-control microfilarial prevalence and modelling assumptions are as in the legend of Table 5.2.

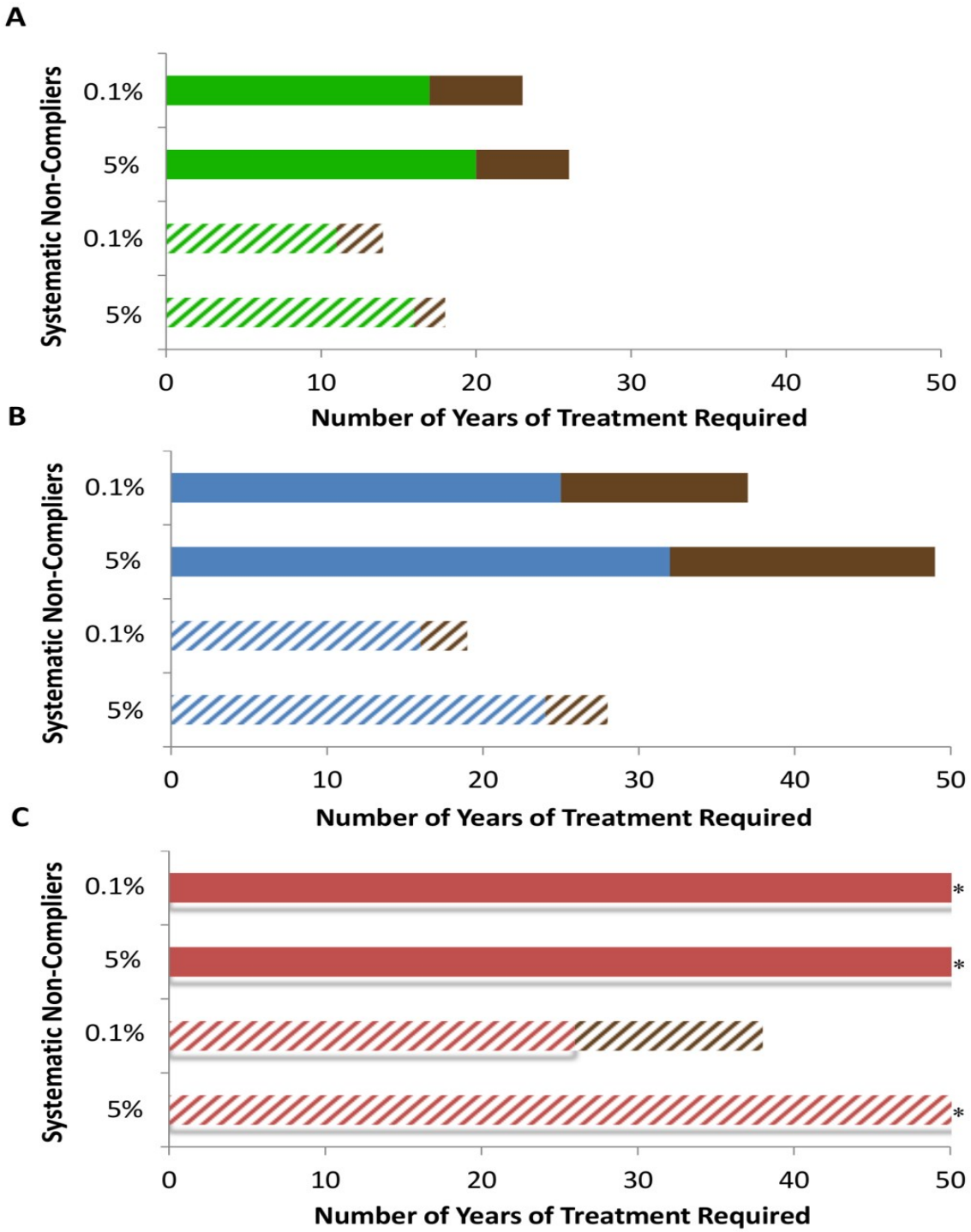

Figure 5.4. Sensitivity of the projected duration of an annual and biannual ivermectin treatment programme for onchocerciasis control to different levels of coverage and systematic non-compliance. *Panels **A**, **B**, and **C** correspond to, respectively, a pre-control endemicity of 40%, 60%, and 80% microfilarial prevalence. Dark brown bars represent the increment in programme duration as a result of a decrease in the assumed therapeutic coverage from 80% to 60%. Annual and biannual ivermectin treatments are indicted by solid and dashed bars respectively. The analysis was performed with a 50-year time horizon and a 7% cumulative reduction in microfilarial production by female adult worms per ivermectin dose.* Operational threshold not attained within the 50 year time horizon.*

Economic Assumptions:

The incremental total cost of starting with, or switching to, biannual treatment was highly sensitive to the relative increase in the cost of biannual versus annual CDTI (Table 5.5). Increasing the discount rate reduced the cost-effectiveness of both annual and biannual CDTI, with this reduction being more pronounced the lower the pre-control endemicity level.

The cost-effectiveness of both annual and biannual CDTI (and the potential cost savings) was substantially reduced by the inclusion of the economic value of the donated ivermectin tablets. However, the cost-effectiveness ratios of annual treatment remained under the World Bank thresholds for this strategy to be considered as cost-effective (Tables 5.6 and 5.7) (World Bank, 1993).

Table 5.5. Sensitivity of the total cost of biannual compared to annual treatment programmes for onchocerciasis control to an increase in the yearly cost of biannual community-directed treatment with ivermectin

Schedule of biannual ivermectin treatment strategy	Pre-control endemicity	Increase in cost (per year) of biannual with respect to annual community-directed treatment with ivermectin	
		40%	80%
Biannual ivermectin treatment implemented from start of the programme		**Ratio of the total costs (biannual/annual)**	
	Mesoendemic	0.99	1.27
	Hyperendemic	1.02	1.31
	Highly hyperendemic	0.98	1.26
Switching to biannual treatment at different levels of microfilarial prevalence in an ongoing annual treatment programme		**Ratio of the additional total costs* (biannual/annual)**	
30% microfilarial prevalence	Mesoendemic	0.99	1.27
	Hyperendemic	1.04	1.34
	Highly hyperendemic	0.85	1.09
20% microfilarial prevalence	Mesoendemic	0.95	1.23
	Hyperendemic	0.97	1.25
	Highly hyperendemic	0.76	0.97
15% microfilarial prevalence	Mesoendemic	0.95	1.23
	Hyperendemic	0.91	1.17
	Highly hyperendemic	0.66	0.85

* The ratio of additional costs is considered from the point of switching from annual to biannual treatment (as opposed to from the start of control). When switching from annual to biannual treatment, infection (microfilarial) prevalence was assumed to be measured at the beginning of the programmatic year (i.e. just before treatment is distributed). Pre-control microfilarial prevalence and modelling assumptions are as in the legend of Table 5.2.

Table 5.6. Sensitivity of the cost-effectiveness of annual and biannual ivermectin treatment programmes for onchocerciasis control to the discount rate, and the economic value of the donated ivermectin tablets

Pre-control endemicity	Cost-effectiveness ratio of annual ivermectin treatment (US$)[†]			Incremental cost-effectiveness ratio of biannual ivermectin treatment (US$) [§]		
Excluding the value of (donated) ivermectin tablets						
	Discount rate			**Discount rate**		
	0%	3%	6%	0%	3%	6%
Mesoendemic	6**	11**	17**	13**	48*	87*
Hyperendemic	3**	5**	9**	5**	31**	61*
Highly hyperendemic	2**	3**	5**	2**	12**	42*
Including the value of (donated) ivermectin tablets						
	Discount rate			**Discount rate**		
	0%	3%	6%	0%	3%	6%
Mesoendemic	51*	97*	156*	846	1,302	1,789
Hyperendemic	26**	49*	80*	408	750	1,118
Highly hyperendemic	19**	29**	42*	16**	334	717

[†] The ratio of the total cost and the total number of DALYs averted (i.e. the cost per DALY averted) of an annual ivermectin treatment programme. [§] The ratio of the incremental cost and the incremental number of DALYs averted by a biannual compared to annual ivermectin treatment programme (i.e. the extra cost per extra health gain). ** Highly cost-effective (< US$40 per DALY averted), * cost-effective (US$40 to US$238 per DALY averted) based on the World Bank cost-effectiveness thresholds (inflated to their 2012 equivalent) (World Bank, 1993). Pre-control microfilarial prevalence and modelling assumptions are as in the legend of Table 5.2.

Table 5.7. Sensitivity of the relative total cost of biannual compared to annual treatment programmes for onchocerciasis control to the discount rate

Schedule of biannual ivermectin treatment strategy and initial level of onchocerciasis endemicity		Ratio of total cost (biannual/annual)			Ratio of total cost (biannual/annual)		
		Excluding the value of (donated) ivermectin tablets			Including the value of (donated) ivermectin tablets		
Biannual ivermectin treatment implemented from start of the programme		**Discount rate**			**Discount rate**		
		0%	3%	6%	0%	3%	6%
	Mesoendemic	1.04	1.13	1.22	1.27	1.38	1.49
	Hyperendemic	1.03	1.16	1.28	1.26	1.42	1.57
	Highly hyperendemic	0.83	1.12	1.34	1.02	1.37	1.64
Switching to biannual treatment at different levels of microfilarial prevalence in an ongoing annual treatment programme		**Discount rate**			**Discount rate**		
		0%	3%	6%	0%	3%	6%
30% microfilarial prevalence	Mesoendemic	1.04	1·13	1.22	1.27	1.38	1.49
	Hyperendemic	1.07	1.19	1.30	1.31	1.46	1.59
	Highly hyperendemic	0.67	0.97	1.22	0.82	1.19	1.49
20% microfilarial prevalence	Mesoendemic	1.00	1.09	1.18	1.23	1.34	1.44
	Hyperendemic	0.99	1.11	1.22	1.22	1.36	1.49
	Highly hyperendemic	0.58	0.87	1.13	0.71	1.06	1.38
15% microfilarial prevalence	Mesoendemic	1.00	1.09	1.18	1.23	1.34	1.44
	Hyperendemic	0.93	1.04	1.14	1.14	1.27	1.40
	Highly hyperendemic	0.48	0.75	1.02	0.59	0.92	1.24

Pre-control microfilarial prevalence and modelling assumptions are as in the legend of Table 5.2

Ivermectin Anti-Macrofilarial Action:

The magnitude of the assumed anti-macrofilarial effect of ivermectin (on rates of microfilarial production by female worms) had little influence on health impact (Chapter 3). However, the larger the assumed effect, the shorter the projected duration of annual MDA (underscoring the desirability of having a truly macrofilaricidal drug, or a drug with a more profound effect on female worm fertility). This consequently decreased the incremental benefit (in terms of the reduction in programme duration) of switching to biannual treatment, particularly in highly hyperendemic areas. Under greater anti-macrofilarial action scenarios, biannual treatment would still considerably shorten projected programme duration, but would not generate programmatic cost savings (Table 5.8).

Table 5.8. Sensitivity of the health impact, total cost and duration of annual and biannual ivermectin treatment programmes for onchocerciasis control to the magnitude of the anti-macrofilarial action of ivermectin

Schedule of ivermectin treatment strategy and initial level of onchocerciasis endemicity		Ratio total of health impact (biannual/ annual)	Ratio total of costs (biannual/ annual)	Projected duration of treatment programme (years)	
				Annual frequency	Biannual frequency
Annual or biannual ivermectin treatment implemented from start of the programme					
	Mesoendemic	1.03	1.26	12	9
	Hyperendemic	1.04	1.38	17	14
	Highly hyperendemic	1.04	1.14	38	22
Switching to biannual treatment at different levels of microfilarial prevalence in an ongoing annual treatment programme					
30% microfilarial prevalence	Mesoendemic	1.03	1.22	11	8
	Hyperendemic	1.04	1.44	16	14
	Highly hyperendemic	1.04	1.09	34	19
20% microfilarial prevalence	Mesoendemic	1.03	1.22	11	8
	Hyperendemic	1.04	1.43	15	13
	Highly hyperendemic	1.04	1.09	32	18
15% microfilarial prevalence	Mesoendemic	1.03	1.22	11	8
	Hyperendemic	1.03	1.39	13	11
	Highly hyperendemic	1.04	1.08	30	17

The analysis was performed with a 50-year time horizon, discount rate of 3% applied both to costs and health benefits, therapeutic coverage of 80%, 0.1% systematic non-compliers, perennial transmission, and 30% cumulative reduction in microfilarial production by female adult worms per ivermectin dose. Costs do not include those incurred by Merck & Co.

5.5 Discussion

These results suggest that annual CDTI has a large and highly cost-effective impact on human health. This is consistent with previous appraisals (Benton, 1998; Remme *et al.* 2006), including a study by Coffeng *et al*. (2013) which estimated that APOC costs US$27 per DALY averted, (this programme wide estimate would include forest areas, which have a different relationship between infection and sequelae; for example generally less blindness is found in forest foci – see section 1.2). Reaching the operational thresholds suggested by APOC (African Programme for Onchocerciasis Control, 2010), in mesoendemic and borderline hyperendemic areas (those close to 60% microfilarial prevalence) is likely to be feasible for 2020/2025 using annual CDTI if coverage and compliance levels are high, in agreement with epidemiological observations (Diawara *et al.* 2009; Tekle *et al.* 2012). However, these observations pertain to foci with seasonal by *Simulium sirbanum* as opposed to perennial transmission.

By contrast, these projections indicate that in initially highly hyperendemic areas (represented here by 80% microfilarial prevalence), it may not be feasible to reach the proposed operational thresholds with annual ivermectin treatment alone, even with high levels of coverage and compliance. This is because, in the absence of vector control, there is substantial transmission between consecutive annual treatments under scenarios of perennial transmission (Chapter 3) (Figure 5.5). Although under these conditions, biannual ivermectin treatment would only have a small additional health impact—and would be deemed less cost-effective than annual treatment in terms of the additional cost per additional DALY averted—it would lead to reduced programme duration.

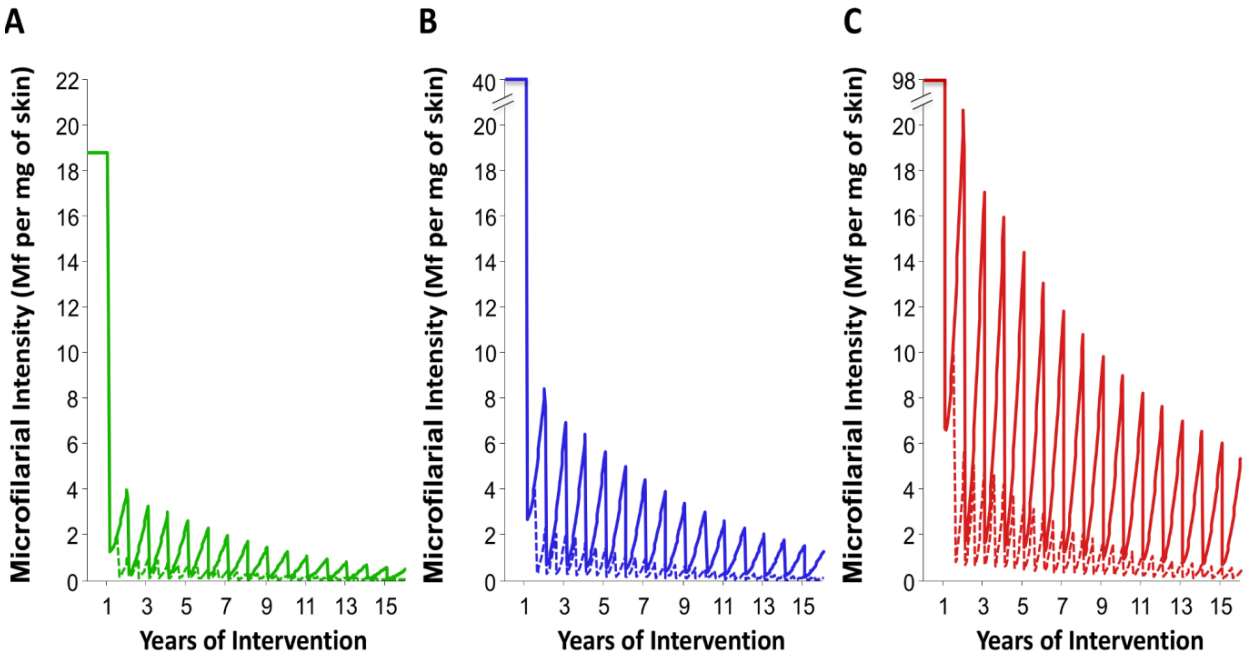

Figure 5.5. A comparison of the impact of annual and biannual ivermectin treatment on onchocercal microfilarial intensity. *Annual and biannual ivermectin treatments are indicated by solid and dashed lines respectively. Panels **A**, **B**, and **C** correspond to, respectively, a pre-control endemicity of 40%, 60%, and 80% microfilarial prevalence. Microfilarial intensity is quantified as the mean (arithmetic) microfilarial load per mg of skin in those aged ≥ 20 years. The analysis was performed assuming a therapeutic coverage of 80%, 0.1% systematic non-compliers, perennial transmission, and a 7% cumulative reduction in microfilarial production by female adult worms per ivermectin dose.*

The impact of biannual treatment was strongly related to pre-control endemicity, with greater projected benefits for higher initial infection prevalence, greatly reducing the residual inter-treatment transmission (Figure 5.5). In areas with lower pre-control endemicity (lower vector biting rates) such transmission becomes less important and biannual treatment has a lesser impact, yet still shorten programme duration (Figure 5.2 and 5.5). These projections also indicate a notable benefit of switching to biannual treatment during an ongoing annual MDA programme (Figure 5.3). This is supported by a recent epidemiological study in the Abu Hamed focus of Sudan, which reported that switching from annual to biannual treatment from 2007 hastened interruption of transmission (Higazi *et al.* 2013), as well as by reports of interruption of transmission in the Wadelai focus of northwest Uganda, where treatment frequency was increased to twice a year from 2006 (Katabarwa *et al.* 2012). This suggests

that the true value of a biannual treatment strategy lies in its potential to accelerate progress towards reaching the elimination goals proposed by the LDNTD and WHO, instead of bringing additional health gains. Therefore, cost-effectiveness ratios (i.e. the cost per DALY averted or health gain within a given time horizon), are not necessarily the most informative metric by which to judge biannual CDTI. This highlights the need for the development of further economic evaluation frameworks, which better account for the long term benefits of elimination, to appraise more appropriately the potential impact of alternative treatment strategies for those NTDs targeted for elimination (World Health Organization, 2013).

5.5.1 Sensitivity analysis

Coverage and Compliance:

The health impact of ivermectin treatment was very robust across a range of different levels of therapeutic coverage and systematic non-compliance. Therapeutic coverage has a large bearing on the projected programme duration and total cost of annual treatment, which is consistent with the results of other modelling studies (African Programme for Onchocerciasis Control, 2010; Winnen *et al.* 2002). However, levels of systematic non-compliance have an even larger influence on the projected incremental cost and programme duration of biannual MDA (Figure 5.4). This has important programmatic implications; in areas where there is low coverage but high compliance, biannual treatment may still provide benefit. This highlights the need to evaluate and understand the determinants of systematic non-compliance in programmatic evaluations (Chapter 2). The deleterious effect of low coverage and high systematic non-compliance increased in areas of high initial endemicity. In highly hyperendemic areas with low coverage and/or high systematic non-compliance, even a biannual treatment strategy may not be sufficient to reach the proposed OTTIS. This highlights the importance of implementing or developing alternative or complementary intervention tools (Taylor *et al.* 2010) such as vector control, macrofilaricidal therapies, more potent microfilaricides, and/or vaccines, as well as of conducting modelling studies to inform how best to combine these according to epidemiological and programmatic setting.

These projections indicate that in communities with only moderate therapeutic coverage of annual CDTI (e.g. 60%), efforts to increase the coverage to a higher level (e.g. 80%) may have a similar (yet smaller) effect than increasing treatment frequency. However, it was

assumed that the level of therapeutic coverage and systematic non-compliance is independent of treatment frequency. Yet it is conceivable that increasing treatment frequency to twice yearly may reduce systematic non-compliance and/or increase coverage because drug distribution would not always occur at the same time each year, with some individuals potentially being consistently missed due to seasonal work. In these circumstances, biannual treatment might have a larger impact than that presented here (provided sufficient efforts are made to maintain high coverage and compliance).

Economic Assumptions:

The Ghana-specific estimate of a 60% increase in the cost (per year) of biannual versus annual CDTI (excluding the value of the donated drug) (Chapter 4) is consistent with values for the increase in cost of biannual drug distribution for lymphatic filariasis control in Africa (Stolk *et al.* 2013). However, this cost will undoubtedly vary among countries and programmatic scenarios. The sensitivity analysis illustrates that it has a large effect on the incremental cost of implementing from the start, or switching to biannual treatment. This highlights the need for countries considering changing to biannual treatment to assess the potential cost increase for their specific situation and other co-endemic infections.

Despite the inclusion of the large economic value of the donated ivermectin tablets, annual CDTI remained cost-effective, although such inclusion did raise the incremental cost of biannual treatment (Tables 5.6 and 5.7). Further examination is necessary of other potential costs associated with increasing treatment frequency incurred by Merck & Co., such as those of establishing new production lines to meet higher demands for ivermectin tablets.

Ivermectin Anti-Macrofilarial Action:

The magnitude of ivermectin-induced anti-macrofilarial effects has an important bearing on the relative benefit of biannual treatment (and possibly drives potential discrepancies between the conclusions of different modelling studies regarding the relative benefit of biannual treatment) (Chapter 2). Under assumptions of a larger cumulative reduction on microfilarial production by adult worms, the relative impact of biannual treatment decreases and ceases to be strongly associated with pre-control endemicity levels. This is because a greater cumulative effect on microfilarial production reduces the level of residual transmission occurring between consecutive annual treatments (Chapter 2). Nevertheless, a biannual

treatment strategy would still shorten programme duration, particularly in highly hyperendemic areas, although it might not generate cost savings (Table 5.8).

5.6. Conclusions

Biannual ivermectin treatment yields only small additional health benefits over those of annual treatment. However, in the context of elimination goals, the benefit of biannual treatment is pronounced, shortening timeframes to reach proposed operational thresholds in the 2020/2025 timeframes. This applies both to scenarios deploying the biannual strategy from the outset, or switching from an existing annual strategy. This effect becomes more pronounced for settings with high pre-intervention endemicity; in highly hyperendemic areas reaching such thresholds would only be possible using biannual CDTI, provided therapeutic coverage and compliance are high. A biannual treatment strategy also reduces the heterogeneity in the projected programme duration among settings with a different pre-control endemicity, and could act to mitigate cross transmission among contiguous onchocerciasis foci, as well as to reduce infection re-introduction into controlled areas. Reductions in programme duration could potentially lead to programmatic cost savings. Projected outputs depend on assumptions of effects of prolonged ivermectin treatment on adult worms, coverage, compliance, and association between infection and disease.

Besides cost, shorter programmes are more attractive to donors, health officials and politicians, and are at a lower risk of disruption by economic and political instability. Notwithstanding these conclusions, the feasibility of increasing from one to two treatments yearly will vary with the specific programmatic circumstances of the country, availability of resources, and incremental cost. The benefit and cost of biannual treatment is particularly sensitive to levels of systematic non-compliance, (i.e. the proportion of the eligible population who never take treatment) stressing the need for programmes to strive for high compliance or at least quantify it, not just focusing on therapeutic coverage, in order to understand the determinants of success or lack thereof when monitoring and evaluating progress towards the LDNTD and WHO elimination goals.

5.7. Limitations

Currently, EpiOncho is parameterised for savannah areas of Africa (Filipe *et al.* 2005). Consequently, conclusions are not necessarily directly generalizable to forest settings, which have different relationships between infection and sequelae, and where onchocerciasis vectors are different members of the *S. damnosum* s.l. complex (section 1.2) (Basáñez *et al.* 2006; Bradley *et al.* 2005; Dadzie *et al.* 1989; Duke, 1990). Additionally, the disease burden associated with disfiguring skin lesions was not quantified, and therefore the overall health impact and cost-effectiveness of CDTI may be underestimated (as discussed in Chapter 3).

A fundamental assumption of the model is that of closed populations; there is no cross transmission or 'spill over' infection between contiguous or otherwise proximate onchocerciasis foci. In reality, this is seldom the case, and in some areas treatment cannot be stopped due to the threat of re-introduction of infection from nearby areas where transmission is more intense, requiring more frequent or longer MDA. This would incur a cost which is not captured in this study. Consequently, the true programmatic value of the potential for biannual treatment to reduce heterogeneity in programme duration among areas with different infection endemicities (different transmission intensities) is likely to be considerably underestimated. Furthermore, this analysis is performed within a 50-year time horizon, and therefore, the true cost of having to continue annual CDTI beyond this point, particularly in highly hyperendemic areas is not captured. Consequently, the potential cost savings generated by biannual CDTI are also underestimated.

Furthermore, it was implicitly assumed that onchocerciasis control is conducted independently from other control programmes. However, onchocerciasis and lymphatic filariasis control activities are often carried out simultaneously. The possible implications of this on the programme costs, drug supplies, donation programmes, and duration of drug distribution were not considered in this analysis. For instance, if MDA frequency were increased for lymphatic filariasis control, it may reduce the relative increase in cost of biannual CDTI for onchocerciasis.

Additionally, the analysis assumed that ivermectin's efficacy remained unchanged for the entire duration of the MDA programmes and does not decrease due to development of ivermectin resistance. Further investigation is needed regarding how sub-optimal responses to

ivermectin (such as those reported in several communities in Ghana (Awadzi *et al.* 2004a; Awadzi *et al.* 2004b; Osei-Atweneboana *et al.* 2011; Osei-Atweneboana *et al.* 2007)), may influence the potential benefit of biannual compared to annual ivermectin treatment.

Moreover, it will be important to develop more comprehensive costing functions, accounting for how the costs of annual and biannual MDA may change with scale (and as mentioned above, be influenced by other related control strategies).

Although the current OTTIS, are supported by the epidemiological and entomological evaluations in Mali and Senegal (Diawara *et al.* 2009; Tekle *et al.* 2012) (for both annual and biannual MDA), further validation / comparison to true transmission breakpoints in different ecological and epidemiology settings is required.

EpiOncho is a deterministic model and it does not account for the influence of random events (which become particularly important at low infection levels). Consequently the potential influence of stochastic process on the time to reach the OTTIS was not captured in this analysis. Though, it should be noted that the current simulations are consistent with epidemiological observations in Mali, Senegal and Nigeria (Diawara *et al.* 2009; Tekle *et al.* 2012; Traore *et al.* 2012), where the OTTIS was reached after 15–17 years of annual ivermectin distribution. Furthermore, the goal was not to predict the time to reach the OTTIS (or elimination) accurately for any particular country, but to investigate the relative benefit of biannual treatment and although stochastic process may cause variations in the estimated number of years to reach the OTTIS, they are unlikely to affect this relative benefit of biannual treatment.

Chapter 6: Conclusions

6.1. Summary of Key Findings

The key findings of this thesis are as follows:

- If ivermectin does not have a large anti-macrofilarial action, as previously assumed in many modelling studies (Coffeng *et al.* 2013; Winnen *et al.* 2002), elimination of onchocerciasis in (highly) hyperendemic areas may not be feasible with annual ivermectin distribution alone.
- The recent estimates of the global burden of onchcoercal disease (Murray *et al.* 2012), which did not include any excess mortality associated with onchocerciasis or prevalent vision loss cases, are being underestimated.
- Although, long term annual ivermectin treatment is highly effective at reducing the morbidity and excess mortality associated with onchocerciasis, its overall impact on microfilarial prevalence and intensity depends strongly on baseline endemicity, treatment coverage and compliance.
- The cost (per year) of biannual ivermectin distribution is approximately 60% higher than the cost of annual treatment. Therefore simply doubling the cost of annual community-directed treatment with ivermectin (CDTI) (as some studies have assumed (Ndyomugyenyi *et al.* 2007)) does not yield a correct estimate.
- Biannual treatment increases the feasibility of, and shortens the timeframes for, reaching the proposed operational thresholds for stopping treatment.
- The benefit and cost of biannual treatment are particularly sensitive to levels of systematic non-compliance.

6.2. Policy Implications

While biannual treatment yields only small additional health benefits over those of annual treatment, in the context of the recent elimination goals, its benefit is pronounced, shortening the timeframes for and increasing the feasibility of, reaching the proposed operational thresholds for stopping treatment. Indeed, in settings with high pre-control endemicity

reaching such thresholds would only be possible by switching to biannual ivermectin treatment. A biannual treatment strategy could also act to mitigate cross transmission among contiguous onchocerciasis foci, as well as to reduce the chance of infection re-introduction into controlled areas. This has important policy implications and implies that increasing the treatment frequency should be considered, particularly in highly hyperendemic areas.

However, as discussed in Chapter 5, it may not always be feasible to increase the treatment frequency, particularly where resources or access to the villages are limited. Additionally the benefit of biannual treatment is highly sensitive to the level of systematic non-compliance, stressing the need for programmes to evaluate treatment compliance as well as therapeutic coverage.

A summary of the principal findings of the thesis was presented at a Mectizan Donation Program (MDP) meeting held in Accra, Ghana, in April 2013 (see Appendix A).

6.3. Future Research Directions

6.3.1. Further model parameterization

EpiOncho is parameterised for the savannah areas of Africa and the results are not necessarily directly generalizable to the forest areas which have a different relationship between infection and sequelae (Basáñez *et al.* 2006; Bradley *et al.* 2005; Duke, 1990). Furthermore, the model's parameters for vector competence, survival, and host choice were those for savannah species of the *Simulium damnosum sensu lato* (s.l.) complex (Basáñez *et al.* 2009; Filipe *et al.* 2005). The influence of different combinations of vectors, such as those in the forest areas, on the impact of ivermectin control and the optimum treatment strategy requires further investigation.

Additionally, the presented results assume that transmission is perennial i.e. occurs all year. Further examination of the influence different seasonal patterns of transmission (and the relative timing of drug distribution), have on the overall impact of long term ivermectin control will be essential to best inform the design of control programmes.

Furthermore, it will be important that a stochastic version of EpiOncho is developed, that can capture the potential influence of stochastic process on the model projections.

6.3.2. Alternative interventions

This thesis focused on evaluating increasing the treatment frequency of ivermectin distribution to twice a year. However a number of alternative strategies are also being developed that require further consideration.

Macrofilaricides:
The macrofilaricidal drugs (such as flubendazole and anti-Wolbachia therapies) that are under development may be useful in several situations,such as; in highly hyperendemic areas; where *Onchocerca volvulus-Loa loa* are co-endemic; in communities where sub-optimal responses to ivermectin have been reported; and mop-up activities in areas close to elimination (Taylor *et al.* 2009). However, further work is needed to investigate the most cost-effective target group and treatment frequency of these drugs.

Moxidectin:
Moxidectin is a highly efficacious microfilaricide, which may cause a more prolonged suppression of adult worm fertility (as it has a longer half-life) (Cotreau *et al.* 2003). It is possible that annual moxidectin may be comparable to biannual ivermectin distribution without the increase in programmatic costs (described in Chapter 4) or the potential strain on programmatic resources. Moxidectin has also been identified as a candidate by MACROFIL, a World Health Organization (WHO) based project established to develop a macrofilaricidal drug to treat onchocerciasis. However, it is important to note that moxidectin's macrofilaricidal effects are unknown and it is not currently licenced for humans.

Foci vector control:
Although wide spread vector control, as used in Onchocerciasis Control Programme in West Africa (OCP), is no longer considered a feasible strategy, foci vector control targeting transmission hotspots may be achievable (and is being conducted in some foci in Uganda (Ndyomugyenyi *et al.* 2007)). A further investigation of the ecological circumstances in which this would be cost-effective is needed.

Vaccines:

There are currently three *O. volvulus* vaccine candidates that have all proven efficacious in animal model systems. However, further investigation of what characteristics will be required for their efficacious use in disease endemic countries (i.e. their target product profile) is needed to help with future development.

6.3.3. The impact of sub-optimal responses to ivermectin treatment

As discussed in section 1.6.3, some communities in Ghana have been identified, in which the adult worms may be becoming resistant to the embryostatic effect of ivermectin (i.e. the adult female worms are resuming reproductive activity earlier than expected in individuals responding well to treatment) (Awadzi *et al.* 2004a; Awadzi *et al.* 2004b; Osei-Atweneboana *et al.* 2011; Osei-Atweneboana *et al.* 2007). Further investigation of how these sub-optimal responses to ivermectin may affect the feasibility of the elimination goals and the best choice of intervention is required. In particular, it is noteworthy that it is possible that increasing the treatment frequency to twice a year could alter the selection pressure for higher levels of suboptimal response to ivermectin. The evolutionary impact of any changes in policy / strategy need to be considered.

6.3.4. Integrated interventions

Neglected tropical disease (NTD) control programmes are becoming more integrated (targeting more than one disease/group of diseases at once), and there is a growing need for modelling studies evaluating interventions to account for this. For instance, onchocerciasis and lymphatic filariasis control activities are often carried out simultaneously. However, the implications of this on the best treatment frequency (for both diseases), total programme cost, and the optimum timing of treatment in relation to different seasonal patterns of transmission have not be explored and require a more holistic modelling approach.

6.4. Conclusion

While the goals of eliminating the public health burden of onchocerciasis will likely be met in areas where long-term annual ivermectin distribution is feasible, those of eliminating the

infection will depend on the epidemiological and programmatic setting, precluding a one-size-fits-all approach to onchocerciasis elimination in Africa.

Although increasing the treatment frequency of ivermectin distribution to twice a year only yields small additional health benefits, in the context of the elimination goals its benefit is pronounced, increasing the feasibility of and shortening the timeframes for reaching the proposed operational thresholds for stopping treatment. Furthermore, these projected reductions in programme duration were found to potentially lead to programmatic cost savings. Additionally, a biannual treatment strategy reduces the heterogeneity in the projected timeframe for elimination among settings with a different pre-control endemicity, mitigating the problem of cross transmission among proximate onchocerciasis foci and the potential for re-introduction of infection into controlled areas. Notwithstanding these conclusions, the feasibility of increasing from one to two treatments yearly will vary with the specific programmatic circumstances.

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Appendix A. Dissemination of Research

Conference and meeting presentations

Oral Presentations

Trans-Atlantic Product Development Partnership for a River Blindness Vaccine: Update Meeting *"Human onchocerciasis: potential long-term consequences of vaccination programmes*" Held in Washington, USA, November 2013.

NTD Modelling Consortium *"An economic evaluation of increasing the frequency of ivermectin treatment for onchocerciasis control in Africa*" Held in Washington, USA, November 2013.

ASTMH 62st Annual Meeting *"An economic evaluation of increasing the frequency of ivermectin treatment for onchocerciasis control in Africa*" Held in Washington, USA, November 2013.

Mectizan Donation Program: Suboptimal Response Meeting "*The role of coverage and compliance, and drug effects on model projections*". Held in Accra, Ghana, April 2013.

Mectizan Donation Program: Suboptimal Response Meeting "*Is the current strategy of annual ivermectin distribution appropriate? Comparisons with biannual treatment*". Held in Accra, Ghana, April 2013.

British Society for Parasitology Spring Meeting: "*Uncertainty surrounding projections of the long-term impact of ivermectin treatment for human Onchocerciasis*". Held in Glasgow, Scotland, April 2012.

Royal Society of Tropical Medicine and Hygiene Research in Progress Meeting: *"Projecting the long-term impact of ivermectin treatment on human onchocerciasis: The importance of modelling assumptions"*. Held in London, England, December 2011.

DIMACS-Workshop on Genetics and Disease Control: "*Cost-Effectiveness Analyses of Drug Resistance Management Strategies for River Blindness"*. Held in Elmina, Ghana, August 2011.

Poster presentations

ASTMH 62st Annual Meeting "*The impact of ivermectin on onchocerciasis and its burden of morbidity and mortality in savannah settings of Africa*" Held in Washington, USA, November 2013.

ASTMH 61st Annual Meeting "*Uncertainty surrounding projections of the long-term impact of ivermectin treatment for human Onchocerciasis*" Held in Atlanta, November 2012.

Publications

Turner, H.C., Churcher, T.S., Walker, M., Prichard, R.K., Osei-Atweneboana, M.Y. and Basáñez, M-G. (2013) Uncertainty surrounding projections of the long term impact of ivermectin treatment on human onchocerciasis. *PLoS Negl Trop Dis* 7: e2169.*

Turner, H.C., Osei-Atweneboana, M.Y., Walker, M., Tettevi, E.J., Churcher, T.S. Asiedu, O., Biritwum, N-K. and Basáñez, M-G. (2013) The cost of annual versus biannual community-directed treatment of onchocerciasis with ivermectin: Ghana as a Case Study. *PLoS Negl Trop Dis,* 7(9): e2452.*

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Turner, H.C., Walker, M., Churcher, T.S., Osei-Atweneboana, M.Y., Biritwum, N-K., Hopkins, A., Prichard, R.K. and Basáñez, M-G. Reaching the London Declaration on Negected Tropical Diseases for onchocerciasis: an economic evaluation of increasing the frequency of ivermectin treatment in Africa. *Under Review.*

Turner, H.C., Walker, M., French, M.D., Blake, I.M., Churcher, T.S. and Basáñez, M-G. Neglected tools for neglected diseases: mathematical models in economic evaluations. *Trends Parasitol Commissioned*.

Press Releases and news articles

Increasing river blindness treatment to twice a year doesn't double cost [http://www3.imperial.ac.uk/newsandeventspggrp/imperialcollege/newssummary/news_19-9-2013-15-52-2].*

* ***Appended overleaf***

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PLOS | NEGLECTED TROPICAL DISEASES

Uncertainty Surrounding Projections of the Long-Term Impact of Ivermectin Treatment on Human Onchocerciasis

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Abstract

Background: Recent studies in Mali, Nigeria, and Senegal have indicated that annual (or biannual) ivermectin distribution may lead to local elimination of human onchocerciasis in certain African foci. Modelling-based projections have been used to estimate the required duration of ivermectin distribution to reach elimination. A crucial assumption has been that microfilarial production by *Onchocerca volvulus* is reduced irreversibly by 30–35% with each (annual) ivermectin round. However, other modelling-based analyses suggest that ivermectin may not have such a cumulative effect. Uncertainty in this (biological) and other (programmatic) assumptions would affect projected outcomes of long-term ivermectin treatment.

Methodology/Principal Findings: We modify a deterministic age- and sex-structured onchocerciasis transmission model, parameterised for savannah *O. volvulus–Simulium damnosum*, to explore the impact of assumptions regarding the effect of ivermectin on worm fertility and the patterns of treatment coverage compliance, and frequency on projections of parasitological outcomes due to long-term, mass ivermectin administration in hyperendemic areas. The projected impact of ivermectin distribution on onchocerciasis and the benefits of switching from annual to biannual distribution are strongly dependent on assumptions regarding the drug's effect on worm fertility and on treatment compliance. If ivermectin does not have a cumulative impact on microfilarial production, elimination of onchocerciasis in hyperendemic areas may not be feasible with annual ivermectin distribution.

Conclusions/Significance: There is substantial (biological and programmatic) uncertainty surrounding modelling projections of onchocerciasis elimination. These uncertainties need to be acknowledged for mathematical models to inform control policy reliably. Further research is needed to elucidate the effect of ivermectin on *O. volvulus* reproductive biology and quantify the patterns of coverage and compliance in treated communities.

Citation: Turner HC, Churcher TS, Walker M, Osei-Atweneboana MY, Prichard RK, et al. (2013) Uncertainty Surrounding Projections of the Long-Term Impact of Ivermectin Treatment on Human Onchocerciasis. PLoS Negl Trop Dis 7(4): e2169. doi:10.1371/journal.pntd.0002169

Editor: Sara Lustigman, Lindsley F. Kimball Research Institute, United States of America

Received November 5, 2012; **Accepted** March 6, 2013; **Published** April 25, 2013

Funding: HCT is funded by an ESRC (Economic and Social Research Council of the UK, http://www.esrc.ac.uk) doctoral studentship (grant ES/I020888/1). TSC is supported by an Imperial College Junior Research Fellowship (http://www3.imperial.ac.uk/juniorresearchfellowships). MW is funded by a Wellcome Trust (http://www.wellcome.ac.uk) project grant (092677/Z/10/Z). MYOA is a European Foundation Initiative for African Research into Neglected Tropical Diseases (EFINTD) research fellow (http://ntd-africa.net/). The research of RKP at the Institute of Parasitology, McGill University is supported by a Regroupement Stratégique grant from FQRNT, Quebec, to the Centre for Host-Parasite Interactions. MGB thanks the Wellcome Trust (grants 085133/Z/08/Z and 092677/Z/10/Z). MYOA and MGB thank the Royal Society-Leverhulme Trust for a Capacity Building Africa Award (http://royalsociety.org/grants/schemes/leverhulme-africa/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Human onchocerciasis, caused by *Onchocerca volvulus* and transmitted by *Simulium* blackflies, is a parasitic disease leading to ocular (vision loss, blindness) and cutaneous (itching, dermatitis, depigmentation) pathology [1,2], as well as to increased host mortality [3,4,5].

The Onchocerciasis Control Programme in West Africa (OCP) started in 1974. The programme was initially based on vector control until, in 1987, ivermectin was registered for human use against onchocerciasis. Thereupon, Merck & Co. Inc. took the unprecedented decision to donate ivermectin for as long as needed to eliminate onchocerciasis as a public health problem [6]. Mass drug administration (MDA) of ivermectin began in some OCP regions in 1988–1989, particularly in extension areas [7]. In some areas of the OCP both antivectorial and antiparasitic measures were combined, whilst in others (mainly in the western extension) ivermectin distribution alone, annually or biannually, was implemented [7,8]. The African Programme for Onchocerciasis Control (APOC) was launched in 1995 to target the 19

Author Summary

Studies in Mali, Nigeria, and Senegal suggest that, in some settings, it is possible to eliminate onchocerciasis after 15–17 years of ivermectin distribution. Computer models have been used to estimate the required duration of ivermectin distribution to reach elimination. Some models assume that annual ivermectin treatment reduces the fertility of the causing parasite, *Onchocerca volvulus*, by 30–35% each time the drug is taken. Other analyses suggest that ivermectin may not have such an effect. We explore how assumptions regarding: a) treatment effects on microfilarial production by female worms (fertility), b) proportion of people who receive the drug (coverage), c) proportion of people who adhere to treatment (compliance), and d) whether people are treated once or twice per year (frequency) affect temporal projections of infection load and prevalence in highly endemic African savannah settings. We find that if treatment does not affect parasite fertility cumulatively, elimination of onchocerciasis in highly endemic areas of Africa may not be feasible with annual ivermectin distribution alone. If two areas have equal coverage but dissimilar compliance, they may experience very different infection load, prevalence and persistence trends. Projections such as these are crucial to help onchocerciasis control programmes to plan elimination strategies effectively.

onchocerciasis endemic countries in Africa not covered by the OCP [8,9]. APOC's strategy involved the establishment of effective and sustainable, community-directed, annual mass ivermectin treatment for all those aged five years and older [10,11]. The programme, initially conceived to end in 2007 [8], and subsequently in 2015 [12], has recently been extended until 2025 with the new goal and commitment for the elimination of onchocerciasis [13].

In addition to OCP western extension areas that were treated twice-yearly (e.g. Senegal [7]), some countries such as Ghana (in the former OCP), and Uganda (in APOC), have adopted a biannual treatment strategy in selected foci; the former because of suspected suboptimal responses to ivermectin treatment [14], and the latter because, in combination with vector control, elimination may be accelerated [15,16].

Ivermectin is a potent microfilaricide, causing a greater than 90% reduction in skin microfilarial load within a few days, and a maximum reduction of 98–99% two months after treatment [17]. Ivermectin also has an embryostatic effect on adult female worms, temporarily blocking the release of microfilariae (mf) [18]. The efficacy of the embryostatic effect is approximately 70%, with the maximum reduction of microfilarial production reached one to two months after treatment [17]. Recuperation of adult worms' fertility occurs slowly from three to four months after treatment onwards [17,18] but may not regain its original level up to 18 months after treatment. (The term fertility is used here to refer to worms producing live, stretched mf, by contrast with females producing oocytes or embryos, which would correspond to worm fecundity [17].)

Recent epidemiological and entomological evaluations conducted in Mali and Senegal suggest that 15–17 years of annual (or biannual) ivermectin distribution (in the absence of vector control) may be sufficient to lead to local onchocerciasis elimination in certain foci [19]. In addition, local elimination may have been achieved with 15–17 years of ivermectin distribution in 26 villages in Kaduna state, Nigeria (the first report of such evidence for the operational area of APOC) [20]. These studies have provided proof of principle that elimination with annual ivermectin distribution may be feasible in some African foci. In 2009, an international expert group convened to discuss the implications of these results [21]. Based on experiences with cessation of onchocerciasis control in West Africa and predictions from mathematical models, the group developed an operational framework for elimination and provisionally defined transmission thresholds, namely, a microfilarial prevalence below 5% in all surveyed villages (and below 1% in 90% of the villages), and a proportion of local simuliid vectors harbouring <0.5 L3 larvae per 1,000 flies [19,21].

Mathematical models such as [22], have been used to assess the feasibility of, and predict the duration of ivermectin distribution required for elimination [23]. In these modelling projections, overall (therapeutic) treatment coverage was varied as part of the sensitivity analysis, and those not taking treatment included a (correlated but unreported) fraction of systematic non-compliers. However, the effect of systematic non-compliers (i.e. the proportion of the population aged five years and older who never take treatment) on the feasibility of elimination was not investigated independently from that of coverage. A crucial conjecture of these projections (based on analysis of a 5-year community ivermectin trial in Asubende, Ghana [24]), was that adult female worms, after temporarily ceasing microfilarial production due to the embryostatic effect of ivermectin, gradually reach a new production level which is reduced irreversibly by an average of 30–35% after each treatment round [25], effectively assuming a cumulative effect of ivermectin on female worm fertility (equivalent to an increasing proportion of worms not contributing to transmission; a sort of 'macrofilaricidal' effect [23,25]). However, another modelling study, using data from a community trial with five biannual treatment rounds in Guatemala [26], did not find evidence for a cumulative effect on microfilarial production [27].

Whether or not ivermectin has a cumulative effect on female worm fertility [28,29] will have important implications for the optimal design of MDA programmes, and given the sparse data that exist, this issue represents an area of considerable uncertainty which needs to be taken into account in modelling studies estimating the long-term impact of ivermectin treatment on parasite populations in humans and vectors.

In this paper, we modify our current onchocerciasis transmission model [30] to explore the uncertainty in modelling projections of the long-term impact of ivermectin on *O. volvulus* populations due to assumptions concerning: a) the effect of ivermectin on mf production by female worms (biological variables), and b) treatment coverage and compliance (programmatic variables). We also explore how these affect the benefit of annual vs. biannual treatment frequency.

Methods

Mathematical Model

We modified our sex- and age-structured deterministic onchocerciasis transmission model [30,31], which describes the rate of change with respect to time and host age of the mean number of fertile and non-fertile female adult worms per host, the mean number of microfilariae per milligram (mg) of skin (mf/mg), and the mean number of infective (L3) larvae per fly. To obtain infection prevalence from infection intensity in humans, we assumed that the distribution of mf among hosts is negative binomial as described in [32]. A detailed description of the model equations is given in Supporting Information Text S1: Protocol S1, *Onchocerciasis Population Dynamics Model*. Parameter definitions

and values can be found in Supporting Information Text S2: Supplementary Tables, Table S1.

Ivermectin Effects

After each dose of ivermectin there is a microfilaricidal effect with 99% efficacy, and a reduction in microfilarial production (embryostatic effect) by fertile female worms [17]. The ivermectin-exposed adult worms are then assumed either to: a) reach a new microfilarial production rate which is reduced by 30% ten months after each treatment round (representing a cumulative effect, depicted in Figure 1A), or b) resume microfilarial production, which ten months after each treatment would reach 70% of its baseline value, i.e. is also reduced by 30% from baseline, but the reduction is not additive (representing a non-cumulative effect, as concluded in [27], and illustrated in Figure 1B). The equations modelling the effect of ivermectin in female worm fertility are described in Supporting Information Text S1: Protocol S2, *Modelling the Cumulative Effect of Ivermectin*. Parameter definitions and values can be found in Supporting Information Text S2: Supplementary Tables, Table S2.

Although the cumulative reduction proposed in [25] was estimated from data corresponding to annual ivermectin distribution [24], it was assumed that in the case of biannual treatments, each 6-monthly treatment causes the same proportional reduction. An analysis of the sensitivity of model outputs to this assumption was conducted following [23]. Ivermectin was assumed to have no macrofilaricidal action (i.e. not to reduce adult worm life-expectancy) at the standard dose used for MDA [17,33,34], and to have intact efficacy, i.e., no sub-optimal response [14] or drug resistance [35] were included.

Treatment Coverage, Compliance, and Frequency

The model is stratified into four treatment compliance classes: a first group of individuals who take treatment every round; two groups who take treatment every other round alternately, and a fourth group who never take treatment. The latter class represents individuals in the community who are systematic non-compliers, as opposed to a situation in which a proportion of individuals miss some treatment rounds (e.g. because they are absent or pregnant at the time of treatment). The proportion of systematic non-compliers was set at 0.1%, 2%, and 5% to investigate its effect on model outputs. These values were chosen to explore potential variability in this parameter. A recent ivermectin compliance study reported that 6% had never taken the drug over the course of eight consecutive treatment rounds [36]. The four compliance groups were assumed not to differ in exposure to vectors (which depends on age and sex according to [30]). Children under five years were not treated in the model as they are not eligible to receive ivermectin.

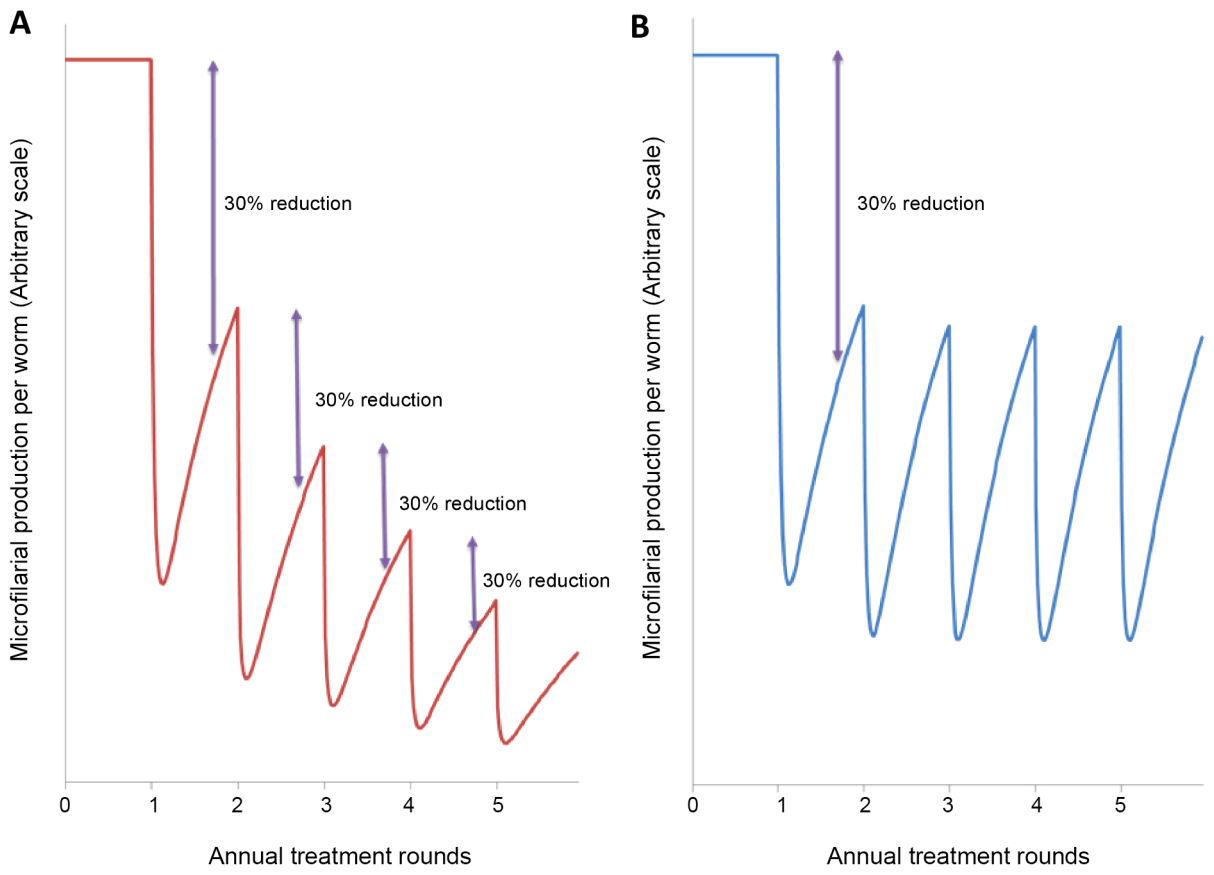

Figure 1. Schematic representation of two different proposed effects of ivermectin on *Onchocerca volvulus* microfilarial production. The schematic represents a closed population of adult worms (i.e., no incoming worms due to transmission or worm death). **A:** Ivermectin is assumed to have a cumulative effect on adult worm fertility by which the microfilarial production of ivermectin-exposed adult worms is reduced by 30% after each treatment round (red solid line). **B:** Ivermectin is assumed not to have a cumulative effect; ivermectin-exposed adult worms resume microfilarial production to 70% of its baseline value ten months after each treatment [17] (blue solid line).
doi:10.1371/journal.pntd.0002169.g001

Model Parameterisation and Examined Outputs

Human age- and sex-structure reflects the demography in savannah areas of northern Cameroon [37,38], as it is in savannah areas of Africa that the prevailing *O. volvulus–S. damnosum* combinations are responsible for the most severe sequelae of onchocerciasis [1,2]. Parameters for vector competence, survival, and host choice were those for savannah species of the *Simulium damnosum* complex (*S. damnosum sensu stricto* and *S. sirbanum*) [30,39], responsible for onchocerciasis transmission in the region [40,41].

The overdispersion parameter for the distribution of adult worms among hosts was as estimated in [27] (see Supporting Information Text S1: Protocol S3, *Mating Probability* and Supporting Information Text S2: Supplementary Tables, Table S3). The parameterisation of the relationship between microfilarial prevalence and load was that for West African savannah areas [32] (see Supporting Information Text S1: Protocol S4, *Microfilarial Prevalence* and Supporting Information Text S2: Supplementary Tables, Table S3). The annual biting rate (ABR) by blackfly vectors was set to 19,000 bites per person per year (well within the range of values recorded in savannah areas [32,40,41]), to achieve a baseline mean microfilarial load of 27 mf/mg (all ages), and of 44 mf/mg of skin in those aged 20 years and above. This resulted in an overall microfilarial prevalence (all ages) of 70%, representing an area of high baseline endemicity. In onchocerciasis, hyperendemic areas are those with overall infection prevalence above 60% [42], but this class can encompass a wide range of transmission and infection intensities. (Note that the mean microfilarial load per mg of skin in those aged ≥20 years here is an arithmetic mean, not a geometric mean of the number of microfilariae per skin snip (ss) (mf/ss) in the same age group, known as the community microfilarial load (CMFL) [43].) Understanding the long-term impact of ivermectin in highly hyperendemic areas is particularly important, as such areas will be those in which controlling the disease has the highest priority (morbidity will be more severe), elimination of the infection reservoir is likely to be more difficult or take longer [23], and from which the infection could reinvade controlled areas.

The model was used to explore the effect of 15 years of (annual or biannual) mass ivermectin distribution on: a) infection intensity defined as mean microfilarial load per mg of skin in those aged ≥20 years, and b) prevalence of microfilaridermia in the overall population. We choose 15 years as a suitable timescale to investigate the impact of long-term treatment of onchocerciasis with ivermectin, motivated by the epidemiological studies described in [19,20]. Since the model is deterministic, the probability of reaching elimination was not investigated.

Sensitivity Analysis

The sensitivity of the above model outputs was explored regarding the following assumptions: 1) cumulative effect of ivermectin on female worm fertility (present vs. absent); 2) overall therapeutic coverage (proportion of the total population receiving ivermectin at each round: 60%, 70%, 80%); 3) proportion of systematic non-compliers (those who never take treatment: 0.1%, 2%, 5%); and 4) treatment frequency (annual vs. biannual). In order to explore the extent to which our results were sensitive to the assumption that biannual treatments each caused the same reduction in fertility of 30% per treatment; we also explored model outputs with a more conservative reduction of 16.5% per 6-monthly treatment (which gives an overall annual reduction of 30%).

Results

Cumulative vs. Non-cumulative Effect of Ivermectin on Microfilarial Production by *O. volvulus*

Model outputs indicate that the assumption of a cumulative impact of ivermectin on microfilarial production by female *O. volvulus* has a substantial effect on projections of long-term ivermectin treatment (Figure 2). Regarding infection intensity in adults aged 20 years and older, there would be a very pronounced decrease partly due to little repopulation of the skin by mf, and partly due to the ensuing suppressed transmission. This is because, under this conjecture, the model assumes that the number of mf produced per female worm per unit time would progressively be reduced to a very low level. By contrast, under the assumption of ivermectin not exerting a cumulative effect on microfilarial production, there is a substantial amount of repopulation of the skin by mf in-between annual treatments, leading to more transmission and a smaller impact on infection intensity.

Annual vs. Biannual Treatment Frequency

Assumptions regarding the operation or absence of a cumulative effect of ivermectin on parasite fertility can also influence the expected relative benefits of annual vs. biannual treatment frequency regarding reductions in infection intensity, prevalence, and transmission. In the presence of a cumulative reduction with each treatment round, there is initially a very marked benefit of the biannual distribution on the reduction of parasitological indicators (as the rate of microfilarial production is rapidly reduced). However, after repeated treatments, there would be much less difference in the long-term impact of ivermectin treatment on microfilarial prevalence compared to an annual treatment strategy (Figure 3A). In the absence of a cumulative effect, biannual treatments are more beneficial both in the short and long terms in

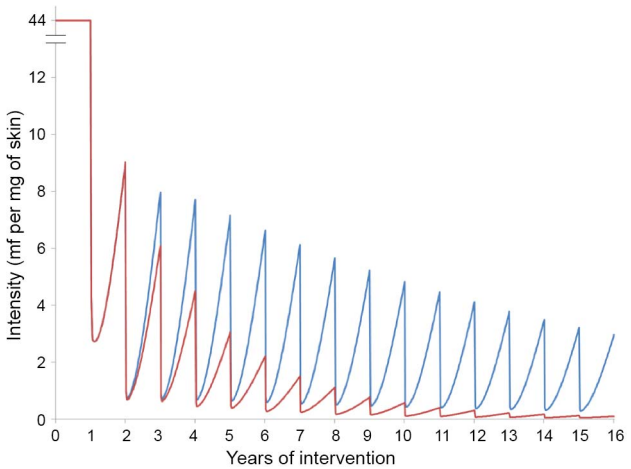

Figure 2. Impact on infection intensity of annual ivermectin distribution under two assumptions of ivermectin effects. Intensity of infection is quantified as microfilarial load per mg of skin in those aged ≥20 years. The red and blue solid lines represent, respectively, model outputs assuming the operation of a cumulative impact on the fertility of *O. volvulus* (illustrated in Fig. 1A), or the absence of such an effect (Fig. 1B). Model calibration corresponds to an ABR of 19,000 (savannah) *Simulium damnosum* bites/person/year; a baseline mean microfilarial load of 44 mf/mg (in those aged ≥20 years); a 70% microfilarial prevalence (all ages); a therapeutic coverage of 80% (overall population); and a systematic non-compliance rate of 0.1%. The demography of the human population is that of northern Cameroon [30,37,38].
doi:10.1371/journal.pntd.0002169.g002

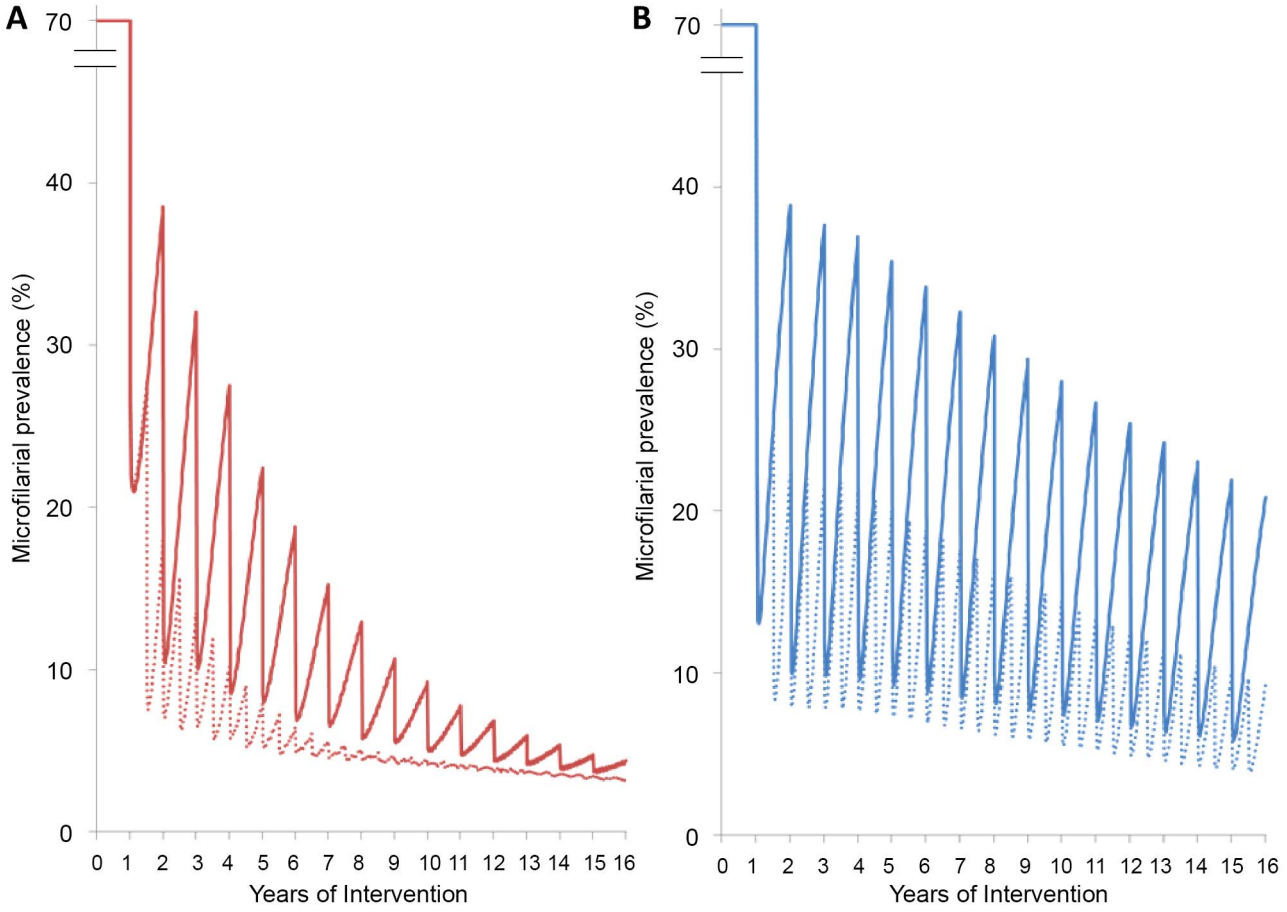

Figure 3. Impact on infection prevalence of annual/biannual ivermectin distribution under two assumptions of ivermectin effects. Solid and dashed lines represent, respectively, annual and biannual treatment frequency. **A:** Red lines correspond to model outputs assuming that ivermectin exerts a cumulative reduction in microfilarial production by the adult female worm. **B:** Blue lines correspond to model outputs assuming the absence of such cumulative reduction. Calibration of the model is as in Figure 2.
doi:10.1371/journal.pntd.0002169.g003

reducing microfilarial prevalence than annual treatments (Figure 3B). With the more conservative 16.5% reduction in female fertility per 6-monthly treatment, the initial benefit of microfilarial prevalence reduction is less pronounced than in the previous scenario, but again, there is relatively little difference in the long-term impact of biannual compared to annual ivermectin treatments (Supporting Information Text S3: Supplementary Figures, Figure S1).

Therapeutic Coverage and Compliance Patterns

Varying the therapeutic coverage in the overall population, and the proportion of systematic non-compliers had a large influence on the infection intensity achieved at the end of the 15th year of ivermectin distribution. An increased overall coverage, or a decreased proportion of systematic non-compliers lead to lower microfilarial loads 12 months after the 15th year of intervention (Figure 4). Under annual treatment, overall coverage had a larger effect on projected infection intensity (Figure 4A) and microfilarial prevalence (Supporting Information Text S3: Supplementary Figures, Figure S2A) than under biannual treatment (Supporting Information Text S3: Supplementary Figures, Figure 4B and Figure S2B). (Because of the nonlinear relationship between infection prevalence and intensity, the proportional reductions in prevalence are smaller.) For instance, under the assumption of a cumulative effect of ivermectin, and for a 5% proportion of non-compliers, increasing therapeutic coverage from 60% to 80% decreased microfilarial load by ~50% for annual frequency compared to 16% for biannual frequency. The corresponding values when no cumulative effect was assumed were ~37% and ~30%. By contrast, the assumed proportion of systematic non-compliers had a more pronounced effect on the impact of biannual treatment delivery. Under the assumption of a cumulative effect of ivermectin, and for a 70% therapeutic coverage, decreasing systematic non-compliance from 5% to 0.1% decreased microfilarial load by ~69% for annual frequency and by ~97% for biannual frequency. The corresponding values when no cumulative effect was assumed were ~23% and ~53%.

Discussion

Cumulative vs. Non-cumulative Effect of Ivermectin on Microfilarial Production by *O. volvulus*

Mathematical models can play a fundamental role in informing control programmes and strategies, but crucially, policy makers must realise that model outputs are highly dependent on implicit and explicit model assumptions [44]. Among the latter and for onchocerciasis in particular, the effects that (yearly or 6-monthly) ivermectin treatments exert on the reproductive biology of *O. volvulus* represent an area of considerable uncertainty, where further research is urgently needed. Although ivermectin's

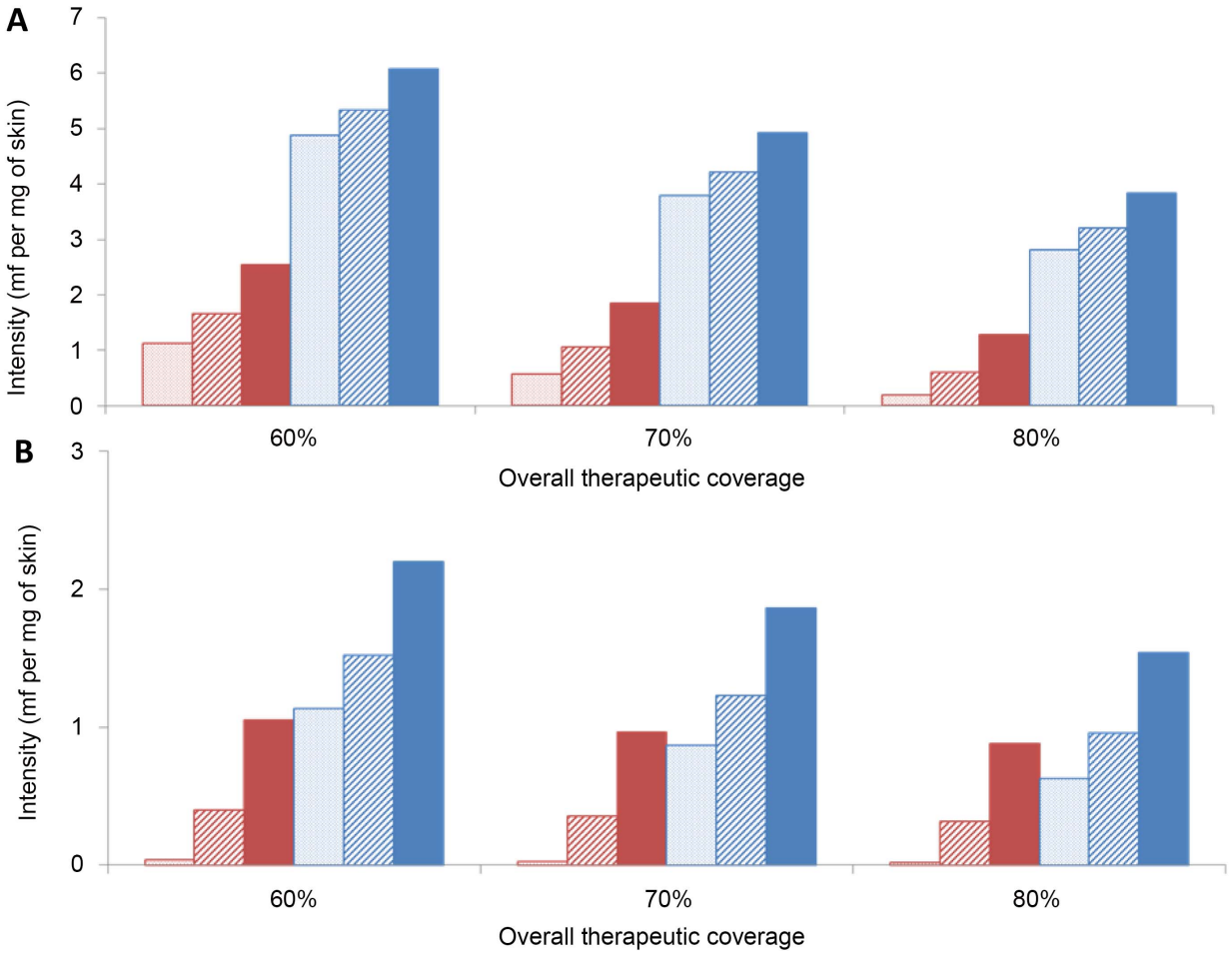

Figure 4. The effect of coverage and compliance on infection intensity after 15 years of ivermectin treatment. Intensity of infection is quantified as microfilarial load per mg of skin in those aged ≥20 years. The values presented correspond to one year after the 15th treatment (for annual frequency, Fig. 4A), or one year after the 30th treatment (for biannual frequency, Fig. 4B). Red and blue bars represent, respectively, a cumulative and a non-cumulative effect of ivermectin on microfilarial production by the female worm. Dotted bars: 0.1% systematic non-compliance; hashed bars: 2% systematic non-compliance; solid bars: 5% systematic non-compliance. Calibration of the model is as in Figure 2. Note the different scale on the vertical axis between 4A and 4B.
doi:10.1371/journal.pntd.0002169.g004

microfilaricidal effect is well established [17], the embryostatic effect and its repercussions on female worm fertility [18]; whether or not such effects on fertility are irreversible [25,28]; the rate of resumption of microfilarial production [17]; and possible effects on intranodular sex ratios and insemination rates [45,46,47], remain poorly understood. An appropriate and updated incorporation of these effects into models, and an understanding of any enhanced macrofilaricidal activity of ivermectin under increased treatment frequency regimes [45,47,48,49], are essential to reliably inform control policy, and fully assess ivermectin efficacy. Our results illustrate that the question of whether or not the drug effects on microfilarial production are cumulative, is highly influential on the projections of the long-term effect of annual or biannual MDA with ivermectin, particularly in areas with high baseline onchocerciasis endemicity.

The data that informed the model in [25], and presented in [24], comprised longitudinal microfilarial load follow up at various time-points after each of five annual treatment rounds in 74 individuals who received all five annual ivermectin doses from 1987 through to 1991 in an early community trial in the savannah focus of Asubende, Ghana [24]. The focus had been under vector control since 1986 during the OCP, and experienced a 70% reduction in parasite exposure during the trial despite antivectorial measures being interrupted for the first three years of ivermectin treatment. Figure 3 of [25] contrasts two model fits explaining the temporal trends in five annual data points of [24], corresponding to (decreasing) microfilarial counts just before each treatment round. The two hypotheses being tested to explain such trends are a null hypothesis of all—ivermectin-exposed—adult worms regaining their full microfilarial productivity vs. an alternative hypothesis of a 35% reduction in productivity with each treatment round. The authors of [25] concluded that the model assuming the alternative hypothesis provided a better fit to the data. However, given that: a) microfilarial loads were measured per skin snip instead of per mg of skin; b) the weight of a skin snip may range between 0.5 and 3 mg; c) lighter snips more likely yield a false negative result, and d) microfilarial counts originated from snips incubated for only 30 minutes in distilled water [24,50] (likely to underestimate microfilarial load as microfilaridermia decreases), there is the possibility of considerable measurement error [5]. This is particularly important regarding the last two data points in the dataset (the most influential for discriminating between the two

hypotheses), as for the last two years of the community trial in Asubende, the study area was receiving full vector control in addition to ivermectin, making it difficult to disentangle the effects of treatment from those of antivectorial measures. (The authors of [25] indicate, however, that the impact of vector control was taken into account in their model.) By contrast, the study in [27], based on the data presented in [26], which did not detect a cumulative effect of ivermectin on the production of microfilariae by female worms, used longitudinal data from 510 individuals (7 times as many as [24]), who took all five 6-monthly doses of ivermectin from 1998 to 1990 in the absence of vector control in Guatemala, with microfilarial loads measured per mg of skin after 24 h incubation [26].

Since our current model is deterministic, we cannot presently explore the probability of elimination. However, comparison of our projections with those of other models is informative. ONCHOSIM projections indicate that with a coverage of 80%, and an initial intensity of 70 mf/ss (in those aged 20 years and older), a minimum of 25 years of annual ivermectin distribution would be necessary to achieve a 99% probability of elimination [21]. In previous projections with the same model [23], the required duration of ivermectin distribution increases steeply and nonlinearly as heterogeneity in individual variation to vector exposure increases. Our model includes age- and sex-dependent exposure to vector bites [30] but does not consider inter-individual variation. The simulations in [21,23] assume that ivermectin has a cumulative effect on the production of mf by female worms, and our results suggest that, in the absence of such an effect, ivermectin would have a less pronounced long-term impact. This indicates that if ivermectin does not have a cumulative effect on the fertility of *O. volvulus*, a longer duration of ivermectin distribution than previously estimated may be required to reach elimination thresholds, especially in areas with a high initial infection intensity and perennial transmission. In some areas of Cameroon that have received 13 years of ivermectin treatment, recent analyses of microfilarial dynamics do not support the operation of a strong cumulative effect of repeated treatments on the microfilarial productivity of female worms [51].

Comparison with provisional thresholds for elimination is also interesting. Operational thresholds based on [19,21] suggest a microfilarial prevalence $<5\%$ in all of the sampled villages, or $<1\%$ in 90% of sampled villages. Our results indicate that microfilarial prevalence would remain above 5% after 15 years of annual or biannual treatment if ivermectin does not affect microfilarial production by *O. volvulus* cumulatively, even with a therapeutic coverage of 80% and only 0.1% of non-compliers (Figure 3B). Our hypothetical baseline infection levels were set at 70% microfilarial prevalence and >40 mf/mg in those aged ≥ 20 years, and the ABR to 19,000 bites per person per year, with perennial transmission. The baseline prevalence in the Senegalese/Malian foci reporting elimination ranged from mesoendemicity to the lower end of hyperendemicity (20% to >60%), and the CMFL from 10 to 48 mf/ss in 16 (27%) of the villages, with CMFL <10 in the remaining 44 (73%) of the 60 surveyed villages. In addition, transmission in these foci is seasonal as opposed to perennial, enhancing the impact of annual treatment on transmission when ivermectin is distributed just before the start of the rains; microfilarial loads are lowest during the transmission season and there are no blackflies around to ingest mf when these start reappearing in the skin [19]. Also, the difference with a biannual strategy would be less pronounced. These factors may have contributed to the feasibility of elimination in these areas and the reported lack of a significant difference between annual and 6-monthly treatment frequency. Likewise, in the foci located in Kaduna state, Nigeria, the median baseline prevalence was 52%, the median CMFL was 4 mf/ss, and transmission was also seasonal [20]. It should be noted that ONCHOSIM projections are consistent with current observations of elimination [19,20,21]. However, as described above, the areas where elimination has currently been achieved had lower baseline endemicity levels, and seasonal vector presence, leading to less transmission during inter-treatment periods. Under these conditions, assumptions of ivermectin effects on adult worms would likely have a lesser effect on models projections.

Our results are compatible with those of other modelling studies [52], which indicate that the higher the transmission intensity, the higher the necessary effectiveness of treatment (a net measure comprising coverage, number of treatment rounds per year and drug efficacy) to reach elimination. However, our study also emphasizes how different modelling assumptions can have profound effects on model outcomes and conclusions (a more extensive summary of the main structural assumptions of different onchocerciasis models is presented in [53]). This further highlights the need, discussed in [44] for helminth modellers to investigate key questions regarding helminth control more collaboratively, exploring the reasons for any disparity between the results of different models using the best available data.

Annual vs. Biannual Treatment Frequency

Biannual ivermectin treatment was found to have a large additional benefit in both reducing microfilarial prevalence and intensity compared to annual treatment when no cumulative reduction in parasite fertility was assumed. When such effect was assumed, the model indicated that there would be an initial substantial benefit (as rates of microfilarial production are reduced quickly) of the biannual strategy, but that there would be relatively little difference in microfilarial prevalence at the end of the 15th year compared to annual treatment (Figure 3A). A possible reason for the pronounced difference between the two treatment frequencies, if ivermectin does not decrease worm fertility cumulatively, is that there would be substantially more transmission between annual than between 6-monthly treatments (distributing the drug every 6 months does not allow the adult worms to regain their fertility to a substantial level if there is perennial transmission, but there may be less additional benefit in seasonal transmission scenarios). Understanding ivermectin's effect on the reproduction and survival of adult worms [17,18,28,29, 45,46,47,48,49] has important policy implications regarding switching to a biannual (or more frequent) treatment strategy in Africa. Three-monthly ivermectin treatments have contributed to acceleration towards local elimination in initially hyperendemic foci in Mexico [54].

Therapeutic Coverage

Varying therapeutic coverage (for fixed non-compliance) had less effect on the impact achieved with a biannual treatment frequency than it had for annual distribution. This can be explained as the model accounts for the fact that if someone misses a treatment round, there is another chance to get treated during that year, ensuring that at least one annual treatment is received. In annual frequency, a missed treatment would result in a gap of at least two years between treatments, allowing microfilaridermia levels to build-up and contribute to transmission in the between-treatments period. This has implications regarding policy decisions in areas that have been found to have low coverage in the past, and highlights the potential benefit of switching to a biannual treatment strategy. In any case, a higher therapeutic coverage would prevent more disease during the intervention as the

intensity of infection would decrease more rapidly. Incidence of blindness [55], and relative risk of excess mortality in sighted individuals [4,5] depend on microfilarial load. It is also important to bear in mind that our model, at this stage, does not include the possibility of sub-optimal response or resistance to ivermectin or financial costs, in which case, the described benefits of a biannual treatment frequency could be very different.

Compliance Patterns

Assumptions regarding the proportion of systematic non-compliers were found to be just as important as those for overall coverage when projecting the long-term impact of ivermectin distribution. The proportion of systematic non-compliance (for a fixed level of therapeutic coverage) was also found to have a marked influence on the impact achieved by a biannual strategy, particularly when assuming a cumulative effect of ivermectin; the higher the non-compliance rate, the smaller the benefit of biannual treatment. This indicates that the effect of systematic non-compliance may not simply be overcome by increasing treatment frequency and has implications when considering switching to a biannual treatment strategy, as two areas with the same overall coverage but different proportion of systematic non-compliers may lead to very different results regarding the feasibility of elimination [56].

As control programmes move towards elimination goals, the proportion of systematic non-compliers in the population becomes increasingly important. Studies of coverage and compliance for lymphatic filariasis treatment have indicated that, in addition to heterogeneity in transmission and vector density, and missed rounds of MDA, continuing transmission seems to be linked to rates of systematic non-compliance [56]. Therefore, when evaluating the progress of elimination programmes, the proportion of, and factors contributing to, systematic non-compliance should be investigated in addition to those determining overall coverage [36,57], as an assessment of the latter on its own may mask reasons behind transmission persistence.

Modelling studies should also routinely vary the proportion of systematic non-compliers in addition to levels of treatment coverage as part of their sensitivity analysis to help understand the impact of prolonged treatment in populations. Although there are some data indicating that treatment compliance may depend on host age and sex (Brieger *et al.* found that older members of the community were more likely to take ivermectin than younger sections of the population, and men were more likely to comply than women in a Cameroon, Nigeria and Uganda multi-centre study [57]), further investigation regarding patterns of systematic non-compliance (i.e. the characteristics of individuals who never take the drug) will be essential to parameterise such modelling studies.

Conclusions and Future Directions

There is substantially more uncertainty surrounding model-derived projections of the long-term impact of, and feasibility of onchocerciasis elimination with ivermectin distribution than previously recognised. This uncertainty arises from an incomplete understanding of the effects of ivermectin on parasite survival, population structure, and reproductive biology, when the drug is administered at the standard dose annually, biannually (or more frequently, e.g. quarterly). Although the results presented in [45,46,47,48,49] would be invaluable to parameterise mathematical models incorporating such effects, further empirical and theoretical research is needed. Regarding the former, there is a need for well-characterized long-term (individual) longitudinal data (including previous treatment history), to estimate reliably the potential macrofilaricidal effects of ivermectin. However, to avoid the potentially confounding effect of ongoing transmission (which may lead to underestimating macrofilaricidal effects, particularly under annual treatment), studies could be conducted in areas where transmission has been interrupted (in geographical or ecological islands by elimination of the local vector [58,59]). In areas near to elimination due to ivermectin distribution alone, rates of skin repopulation by mf could be investigated by fitting models to these data under a variety of ivermectin effects assumptions. Regarding the more theoretical aspects, a more adequate formulation of the parasite's mating probability in light of drug effects, decreasing male to female sex ratios [60], and changes in parasite distribution resulting from prolonged treatment [61] would also be important for assessing the feasibility of elimination.

Our results indicate that in areas with high baseline endemicity and perennial transmission, 15 years of annual or biannual treatment with ivermectin may not be sufficient to bring infection levels below potential elimination thresholds. Further incorporation of ivermectin effects into models; comparison of perennial vs. seasonal patterns of transmission; consideration of other *O. volvulus–Simulium* combinations; calibration of models for a wide range of baseline endemicity levels; assessment of patterns of treatment coverage and compliance; and inclusion of parasite genetic structure regarding sensitivity to ivermectin, will be essential to evaluate uncertainty surrounding model-derived projections. This, together with cost-effectiveness analysis, and development of stochastic frameworks will be crucial for informing control policy regarding annual vs. biannual treatment strategies in Africa, and for exploring the feasibility of elimination in foci with varying degrees of baseline endemicity. Finally, whether prolonged ivermectin treatment has a profound effect on the parasite's reproductive fitness has implications for the risk of ivermectin resistance evolving [35], and the risk of resurgence when treatment ceases. This highlights the importance of post-control surveillance in those foci where treatment is deemed to have been sufficiently successful to be stopped [62,63,64].

Supporting Information

Text S1 Model Description.
(PDF)

Text S2 Supplementary Tables.
(PDF)

Text S3 Supplementary Figures.
(DOC)

Acknowledgments

We thank all members of the Helminth Ecology Research Group at Imperial College London for valuable comments on preliminary versions of the results presented in this paper.

Author Contributions

Conducted the modelling: HCT. Advised on the modelling and commented on the manuscript for intellectual input: TSC MW MGB. Conceived the study: MGB. Read and approved the final, submitted version of the manuscript: HCT TSC MW MYOA RKP MGB. Wrote the paper: HCT TSC MW MGB.

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PLOS | NEGLECTED TROPICAL DISEASES

The Cost of Annual versus Biannual Community-Directed Treatment of Onchocerciasis with Ivermectin: Ghana as a Case Study

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Abstract

Background: It has been proposed that switching from annual to biannual (twice yearly) mass community-directed treatment with ivermectin (CDTI) might improve the chances of onchocerciasis elimination in some African foci. However, historically, relatively few communities have received biannual treatments in Africa, and there are no cost data associated with increasing ivermectin treatment frequency at a large scale. Collecting cost data is essential for conducting economic evaluations of control programmes. Some countries, such as Ghana, have adopted a biannual treatment strategy in selected districts. We undertook a study to estimate the costs associated with annual and biannual CDTI in Ghana.

Methodology: The study was conducted in the Brong-Ahafo and Northern regions of Ghana. Data collection was organized at the national, regional, district, sub-district and community levels, and involved interviewing key personnel and scrutinizing national records. Data were collected in four districts; one in which treatment is delivered annually, two in which it is delivered biannually, and one where treatment takes place biannually in some communities and annually in others. Both financial and economic costs were collected from the health care provider's perspective.

Principal Findings: The estimated cost of treating annually was US Dollars (USD) 0.45 per person including the value of time donated by the community drug distributors (which was estimated at USD 0.05 per person per treatment round). The cost of CDTI was approximately 50–60% higher in those districts where treatment was biannual than in those where it was annual. Large-scale mass biannual treatment was reported as being well received and considered sustainable.

Conclusions/Significance: This study provides rigorous evidence of the different costs associated with annual and biannual CDTI in Ghana which can be used to inform an economic evaluation of the debate on the optimal treatment frequency required to control (or eliminate) onchocerciasis in Africa.

Citation: Turner HC, Osei-Atweneboana MY, Walker M, Tettevi EJ, Churcher TS, et al. (2013) The Cost of Annual versus Biannual Community-Directed Treatment of Onchocerciasis with Ivermectin: Ghana as a Case Study. PLoS Negl Trop Dis 7(9): e2452. doi:10.1371/journal.pntd.0002452

Editor: John Owusu Gyapong, University of Ghana, Ghana

Received February 28, 2013; **Accepted** August 13, 2013; **Published** September 19, 2013

Funding: HCT is funded by an ESRC (Economic and Social Research Council of the UK, http://www.esrc.ac.uk) doctoral studentship (grant ES/I020888/1), and received an Overseas Institutional Visit Award for the work in Ghana. MYOA is a European Foundation Initiative for African Research into Neglected Tropical Diseases (EFINTD) research fellow (http://ntd-africa.net/). MW is funded by a Wellcome Trust (http://www.wellcome.ac.uk) project grant (092677/Z/10/Z). TSC is supported by an Imperial College Junior Research Fellowship (http://www3.imperial.ac.uk/juniorresearchfellowships). MGB thanks the Wellcome Trust (http://www.wellcome.ac.uk) (grants 085133/Z/08/Z and 092677/Z/10/Z). MYOA and MGB hold a Royal Society-Leverhulme Trust Capacity Building Africa Award (http://royalsociety.org/grants/schemes/leverhulme-africa/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Human onchocerciasis or river blindness is a neglected tropical disease (NTD) caused by the parasitic filarial nematode *Onchocerca volvulus* and transmitted by the bites of *Simulium* blackflies [1]. In addition to ocular pathology (vision loss, blindness), and increased host mortality [2,3], onchocerciasis also causes disfiguring skin lesions and severe dermal itching that can drastically impair an individual's quality of life [4]. In 1987, ivermectin was registered for human use against onchocerciasis, and Merck & Co., Inc. took the unprecedented decision to donate ivermectin for as long as needed to eliminate onchocerciasis as a public health problem [5].

Two major onchocerciasis control programmes have been launched in Africa. The former was the Onchocerciasis Control Programme in West Africa (OCP), which started in 1974 and closed in 2002, and was initially based solely on vector control until ivermectin was licensed for human use in 1987. For the most part, the OCP used an annual treatment strategy (alone or in combination with antivectorial measures), but in the Western extension, some foci were treated biannually in the absence of vector control [6,7]. Currently, the former OCP countries

Author Summary

The African Programme for Onchocerciasis Control (APOC) has recently been extended until 2025, with renewed commitment towards onchocerciasis elimination. This aim is aligned with the goals stated by the World Health Organization and the London Declaration on Neglected Tropical Diseases in January 2012. Switching from annual to biannual (twice yearly) ivermectin distribution might increase the feasibility of onchocerciasis elimination in some African foci. However, relatively few communities have received biannual treatments in Africa, and there are no cost data associated with increasing ivermectin treatment frequency at a large scale, essential pre-requisites to provide reliable information for evidence-based decision making regarding adoption of a biannual treatment strategy. Therefore, we undertook a study to estimate costs associated with biannual compared to annual ivermectin delivery in Ghana, which since 2009 has implemented a biannual treatment strategy in selected priority areas. Our results indicate that the cost of biannual ivermectin treatment per year is approximately 60% higher than the cost of annual treatment. This study provides tangible evidence of the different costs associated with annual and biannual ivermectin treatment, which can be used to inform economic evaluations and policy decisions regarding the optimal treatment frequency required to eliminate onchocerciasis in Africa.

undertake their own national onchocerciasis control programmes. The African Programme for Onchocerciasis control (APOC) was launched in 1995 and it has recently been extended to 2025 [8]. It targets the 19 onchocerciasis endemic countries in Africa that were not covered by the OCP (though three of them, Kenya, Rwanda, and Mozambique, were found not to be endemic) [9]. APOC's predominant strategy involves annual, community-directed treatment with ivermectin (CDTI) in areas where the prevalence of onchocercal nodules is greater than 20%, for all those aged five years and older (excluding pregnant or breastfeeding women in the first week after delivery) [9,10].

Based on the experience in Uganda [11], and the success achieved in most onchocerciasis foci in the Americas [12], there have been recent discussions of switching to biannual treatments (twice yearly) to increase the feasibility of elimination. In the past, only a small number of foci within the OCP (such as River Gambia in Senegal [7]) have received biannual treatment in Africa, and therefore there are no ground-truth data on the cost associated with increasing the treatment frequency to twice per year on a large scale. (In Uganda, the cost of biannual CDTI was simply estimated by doubling that of the annual treatment [11].) Motivated by ivermectin efficacy studies suggesting sub-optimal responses of *O. volvulus* to the drug [13,14,15], Ghana (an ex-OCP country), has recently adopted a biannual treatment strategy at a large scale [15].

In Ghana, onchocerciasis is endemic in 9 out of 10 regions with a total at-risk population of approximately 3.2 million [16]. Responsibility for ivermectin distribution—which occurs in 73 districts—was devolved from the OCP to Ghana in 2002 (under the supervision of APOC). Since 2006, onchocerciasis control has been implemented in the context of the Neglected Tropical Diseases Programme (NTDP) [16], and in 2009, 40 (55%) districts started using a biannual ivermectin distribution strategy. The decision regarding which areas should change to the biannual treatment strategy was based on the combined results of rapid epidemiological mapping of onchocerciasis (REMO) conducted in Ghana in 2009, parasitological evaluation via skin snipping and determination of microfilarial prevalence, and entomological evaluations (according to unpublished results of the Ghana onchocerciasis mapping exercise conducted in 2009, and the REMO report summarised in 2010). Areas with an infection prevalence in the adults above 20%, were allocated to a biannual treatment frequency considering also a buffer zone of 20 Km around these CDTI priority areas. Therefore, NTDP decisions as to whether to allocate districts to annual or biannual CDTI were not made on a priori criteria of associated costs but only based on transmission criteria.

In this paper, we report the results of a study undertaken to estimate the costs associated with annual (the standard strategy) vs. biannual CDTI (the newly adopted strategy) in Ghana. We also assess some factors that may hamper the scaling up of treatment frequency at a large scale given that other countries in the region may consider switching from annual to biannual ivermectin distribution.

Methods

Ethics Statement

Ethical approval for the study in Ghana was obtained from Imperial College Research Ethics Committee (ICREC) and the Ethics Review Committee (ERC) of the Ghana Health Service (GHS).

Description of Study Areas

The study focused on the Brong-Ahafo and Northern regions in Ghana. In the former, data were collected in the Wenchi district where CDTI takes place annually; the Pru district and the

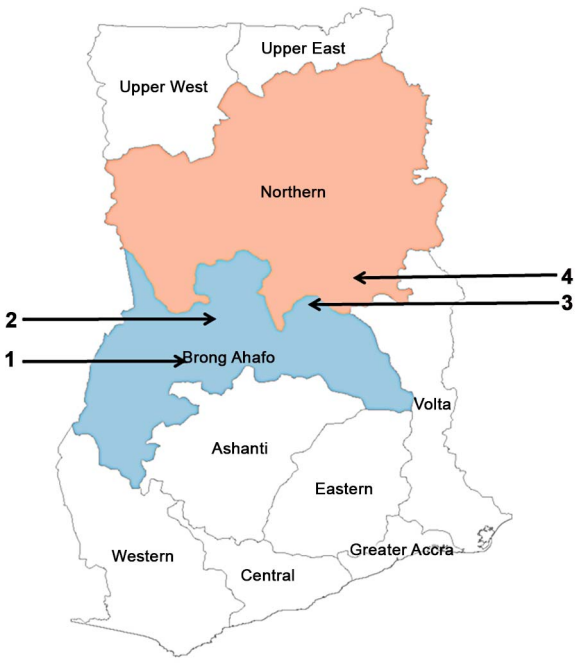

Figure 1. Map of Ghana indicating the sampled regions and districts. The Brong-Ahafo and Northern regions are highlighted in light blue and light pink respectively. 1-Wenchi, 2-Kintampo North, 3-Pru, 4- Kpandai. Figure prepared by Mr Simon O'Hanlon (Imperial College London).
doi:10.1371/journal.pntd.0002452.g001

Table 1. Description of ivermectin treatment in the areas where cost data were obtained in Ghana.

Region	District	Treatment Frequency	Number of Persons Treated Per Year	Overall Therapeutic Coverage (%)[a]	Size (km^2)
Brong-Ahafo	Wenchi	Annual in all communities	27,881	90.43	3,494
Brong-Ahafo	Kintampo North	Biannual in all communities	57,802	82.10	5,108
Brong-Ahafo	Pru	Biannual in all communities	68,506	88.08	2,195
Northern	Kpandai	Annual in 122 (55%) and biannual in 100 (45%) of 222 communities[b]	90,183	79.10	1,772

[a]For the Wenchi and Kpandai districts, therapeutic coverage estimates were taken directly from national records pertaining to the last treatment round of 2010. For the Pru and Kintampo North districts, coverage estimates were derived from an average of two treatment rounds (the last round of 2010 and the first round of 2011).
[b]A biannual strategy is used in 15 of 76 (20%) communities in the sampled sub-district, whereas the remainder 80% receive treatment annually. Therefore, the costs are likely to reflect more closely those of annual rather than biannual distribution.
doi:10.1371/journal.pntd.0002452.t001

Kintampo North district, where CDTI is taking place biannually, and in the latter, data were also collected in the Kpandai district, where a mixed strategy (some communities being treated annually and others biannually) is used (Table 1). These districts were selected partly based on logistics at the time of the study, and partly because already established relationships with the GHS at the district and sub-district levels would ensure collection of accurate data via the purposely designed questionnaires (see below). Figure 1 shows the locations of the districts where the study was conducted. As stated earlier, decisions to switch to a biannual treatment frequency were based on infection and transmission criteria alone, so there were no obvious reasons why the decision to change treatment frequency would have been influenced by the local district-specific programme cost.

Data were collected at various levels in the organization of the GHS. Firstly, information was gathered by conducting semi-structured interviews at the headquarters of the NTDP in Accra, and at the Regional Health Service directorates in the Brong-Ahafo region. Secondly, districts (and sub-districts where appropriate) were chosen to represent a range of geographical sizes, and population densities (Table 1). Thirdly, community drug distributors (CDDs) were interviewed in at least three communities in each district.

Perspective

In this study, the costs under investigation were those borne by the health care providers (such as the GHS, the major in-country partners, and the local communities). Therefore the cost of drug manufacture and transport to Ghana were excluded. Only data on the cost of CDTI were collected; costs associated with individual, clinic-based treatment with ivermectin were ignored.

Data were collected on both the financial and economic costs of CDTI. Financial costs are those where a monetary transaction has taken place for the purchase of a resource. Economic costs also include, in addition to the financial costs described above, estimates of the monetary value of goods or services for which no financial transaction has taken place. Therefore, economic costs also account for the value of goods or services which could have been used for another purpose (opportunity costs). Examples of resources which have no financial costs but do have important economic costs are the 'free' use of building space provided by the Ghana Ministry of Health, the use of donated vehicles, and the time devoted to CDTI by unpaid CDDs. The costs associated with CDTI arise from various programmatic activities as outlined in Box 1.

Data Collection

Data collection was organized at the national, regional, district, sub-district and community levels and involved interviewing key personnel and scrutinizing national records. Data collected at the national level included records of funds provided by non-governmental organizations (NGO) such as Sightsavers (http://www.sightsavers.org/), and others such as APOC (managed by the World Bank and implemented by the World Health Organization) (http://www.who.int/apoc/en/), among others. Given these multiple sources, it would have been most interesting to obtain a detailed breakdown of the relative contribution of each organization to the funding of onchocerciasis control in Ghana. Unfortunately, even at the national sampling level, it was rarely possible to separate the costs by their funding source. This, however, did not affect the study, which focused on the aggregate cost of onchocerciasis control. The costs collected were incurred in the year 2011. At each level, costs were collected according to different resource types (Box 2) using an approach based on methods described by McFarland *et al.* [17] and the UNAIDS guidelines for costing studies [18]. First, the total gross expenditure on a resource (per year) was calculated from national records and/

Box 1. Programmatic Activities (partly based on [17])

- **Drug Distribution Chain:** the process of getting the drugs from where they entered the country to the target population
- **Mobilization and Sensitization:** promotion, information dissemination and advocacy related to the project
- **Training of Volunteers:** training of community drug distributors (CDDs) (includes the costs incurred by both the trainers and the trainees)
- **Other Training:** all other training at whatever level (includes the costs incurred by both trainers and trainees)
- **Reporting:** the preparation and transmission of reports
- **Surveillance and Evaluation:** surveillance of the disease and treatment distribution at all levels
- **All Other Administration:** all other general office administration
- **Other Project Activities:** all other activities not already mentioned above

or questionnaires. Second, the most appropriate person(s) to answer questions on how the resource is used for activities relating to onchocerciasis control was selected for interview. Third, the interviewee was asked to indicate what fraction of time the resource was used for onchocerciasis control over the year (this was corroborated by multiple sources where possible). Multiplication of the total gross cost and fraction of time attributable to onchocerciasis control yielded an estimate of the recurrent yearly cost for a resource (such as an employee). The cost of capital resources—goods that last for more than one year, such as cars and computers—were estimated in a similar fashion, but the gross cost was spread over the average useful lifetime of the resource (a technique known as 'annualization') to arrive at an average yearly cost [18]. (An annualization and discount rate of 3% was used to calculate the economic costs of capital resources [19].) The average useful lifetime of all capital goods was assumed to be five years, in line with the value estimated by McFarland *et al.* [17] and corroborated by study participants at the national level. However, the sensitivity of the results to this assumption was investigated by varying the average useful lifetime between 5 and 8 years [20]. The annual cost of building space was estimated as the equivalent market rental value for the space being used for the control programme [18].

The interviewee was also asked to estimate the fraction of time that the resource was used for itemized onchocerciasis control programmatic activities (Box 1). In addition, in districts receiving ivermectin biannually, the interviewees were asked to describe how their time spent on different CDTI activities had changed since increasing the treatment frequency to twice per year, and to indicate which of the CDTI activities are repeated for both treatment rounds.

At each level, and where relevant, interviewees were given the opportunity to express whether they had encountered any specific difficulties with the increasing of treatment frequency.

Box 2. Resource Types (partly based on [17])

- **Transportation (Capital Costs):** the capital costs associated with vehicles (e.g. the annualized[a] cost of motorbikes and cars)
- **Transportation (Recurrent Costs):** the recurrent costs associated with transport (e.g. fuel, insurance, maintenance, repairs, and rental costs)
- **Personnel:** the recurrent costs associated with paying salaries to employees (including any supplements or other benefits of employment)
- ***Per Diems*:** the recurrent costs associated with daily allowances (*per diems*)
- **Supplies and Equipment (Capital Costs):** other capital costs associated with a project, (e.g. annualized[a] costs of computers, photocopiers, and generators etc.)
- **Supplies and Equipment (Recurrent Costs):** the recurrent costs associated with project activities and general office running
- **Overheads:** the recurrent indirect costs associated with a project's specific utilities charges, building rental or equivalent
- **Volunteer Community Drug Distributor (CDD) Time:** the monetary value of the donated time of CDDs and other community members in implementing community directed treatment with ivermectin (CDTI)

[a] The annual share of the initial cost of capital equipment

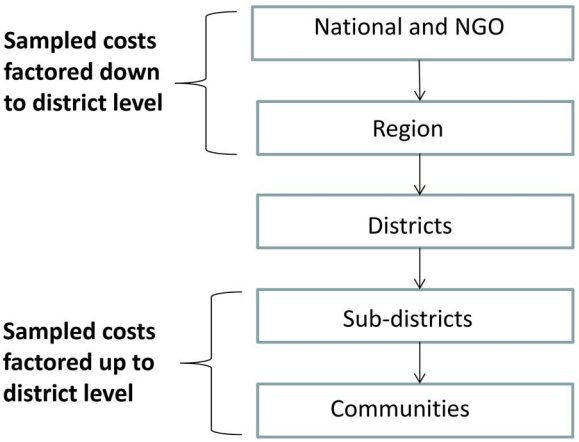

Figure 2. Organization levels at which data on cost of ivermectin distribution were collected.
doi:10.1371/journal.pntd.0002452.g002

Data Analysis

Costs collected at the national and regional levels, were factored down and costs from the sub-district and community levels factored up, with the aim of arriving at a value for the cost per person treated per year in each district (Figure 2). This is described for each of the levels below.

National costs. Of the 73 districts in Ghana where ivermectin is distributed, 40 (55%) are implementing biannual treatment. Consequently, when allocating the national costs to the districts, the costs were weighted according to the district's frequency of treatment. Based on responses to questionnaires, scrutinizing of national records, and conduction of semi-structured interviews, it was estimated that districts treating biannually were responsible for 70% of the total national cost. Separate costs (according to annual or biannual treatment) were allocated equally across districts receiving a certain treatment frequency. Based on interviews at the headquarters of the NTDP and the McFarland *et al.* study [17], it was assumed that the main drivers of the national costs were independent of target population size and therefore we did not adjust the national costs by the size of districts' target populations.

Regional costs. These were distributed among districts using the same frequency of treatment-based weighting as used for the national costs. Due to logistic reasons on the terrain, it was only possible to estimate regional costs from one of the two regions from which districts were sampled. Thus, the costs incurred by the Northern region were assumed to be the same as those estimated from data pertaining to the Brong-Ahafo region.

Sub-district costs. In each district included in this study one sub-district was sampled. The costs incurred by the sampled sub-districts were multiplied by the number of sub-districts within each district to aggregate the costs to the district level.

Community costs. In each district included in this study three communities were sampled. In each sampled community, questionnaires were administered to the CDDs to ascertain to how many people they distributed ivermectin, and whether they received compensation from the district (this was corroborated at the local district health centres). Additionally, the opportunity cost of the volunteer CDDs' donated time was estimated by asking CDDs how much time they spent distributing the drug each treatment round. This donated time was converted to an

equivalent number of 8-hour working days, which were valued according to the minimum wage in Ghana in 2011 (3.73 Ghana Cedis (GHC) per day [21]). This figure was reported to be equivalent to the daily wage of a hired farmland worker in the Brong-Ahafo region, the occupation of the majority of the interviewed distributors, and was subsequently used to estimate the value of the CDDs donated time across each district. However, to place a precise value on a CDD's donated time is difficult and whether or not it should be included is a matter of debate. Furthermore, the daily wage of a hired farmland worker can vary from district to district, and especially from region to region [20,22]. Therefore, we calculated the economic cost both including and excluding CDD's donated time, and investigated the sensitivity of the results to the assumed daily wage (increasing or decreasing it by GHC 1.00).

Currency conversion. All costs were converted from the Ghanaian local currency (GHC), to United States dollars (USD), using the average 2011 exchange rate of USD 1.00 to GHC 1.58 [23]. Reported costs from other studies were also converted to 2011 US dollars (using a consumer price index inflation calculator [24]) to allow for valid comparison with our results.

Results

Table 2 shows the estimated financial and economic costs—including and excluding volunteer CDDs' time—of CDTI in the four sampled districts. The majority of the costs associated with CDTI were financial, with the extra economic cost per person per year (excluding CDDs' time) only adding USD 0.01–USD 0.03 (this includes the value of donated vehicles and use of free building space).

The estimated economic cost (excluding CDDs' time) of annual treatment in Wenchi district is USD 0.40 per person per year. The economic costs (excluding CDD's time) of biannual treatment in the Pru and Kintampo North districts are approximately 50–60% higher (USD 0.60 and USD 0.64 per person per year respectively) than the corresponding annual costs. The estimated economic cost (excluding CDDs' time) for Kpandai district—which uses a combination of an annual and biannual strategy (see Table 1 for description)—is USD 0.43 per person per year. These results were not sensitive to the assumed average useful lifetime of capital goods; changing this from 5 to 8 years only changed the cost per treatment by a maximum of USD 0.015.

Costs Disaggregated by Resource Type and Programmatic Activity

Figure 3 depicts the cost of onchocerciasis control by CDTI disaggregated by resource type in the four sampled districts. The largest proportion of the total cost was associated with the payment of personnel. Recurrent transportation costs, such as the costs of fuel and vehicle maintenance, were the next most costly resource and showed the most variation among districts.

Figure 4 depicts the cost of CDTI-based onchocerciasis control disaggregated by programmatic activity in the four sampled districts. Surveillance and evaluation incurred the highest cost, followed by the drug distribution chain. For Pru and Kintampo North districts, the data show a noticeable increase in the reporting cost compared to Wenchi district.

Community Distributors

From the pooled community data, it was estimated that there is one CDD for every 390 people and they spend an average of 61 hours distributing ivermectin each treatment round. The above value was used with data on the number treated in each district (Table 1) to estimate the total amount of time CDDs spend distributing the drug across the whole district. This increased the economic cost by USD 0.046 per person per year when treating annually, and by USD 0.092 when treating biannually (Table 2). This result was robust to the assumed daily wage of a hired farmland worker, which when increased or decreased by GHC 1.00, only changed the economic cost of CDD per treatment by plus or minus USD 0.012.

The CDDs reported receiving an average equivalent of USD 3.17 in compensation for attending the distribution training sessions (which are conducted before each treatment round), and between USD 3.17 and USD 9.52 after distributing the drug. In this analysis, it was assumed that each distributor received the average (arithmetic mean) of the reported values (a total of USD 9.96 in compensation for both training and distribution for each treatment round).

Reported Difficulties

The implementation of a large-scale, mass biannual ivermectin treatment strategy was reported at the district and sub-district level as being well received and perceived as sustainable in the future. However, the disease control officers at the district health centres in the sampled districts in which biannual treatment is being implemented, reported that increasing the treatment frequency to twice per year substantially increased the workload by increasing

Table 2. Financial and economic costs (USD[a]) per person treated per year in each district.

Frequency of CDTI[b]	Annual	Biannual	Biannual	Mixed[c]
Cost type	**Wenchi**	**Kintampo North**	**Pru**	**Kpandai**
Financial cost	0.39	0.62	0.58	0.40
Economic cost (excluding volunteer CDD's[d] time)	0.40	0.64	0.60	0.43
Economic cost[e] (including volunteer CDD's time)	0.45	0.73	0.69	0.50

[a]USD: US Dollars.
[b]CDTI: Community-directed treatment with ivermectin.
[c]Data from Kpandai district reflect a combination of annual (in 61 of 76 (80%) of the communities in the sampled sub-district) and biannual treatment frequency (see Table 1 and main text).
[d]CDD: Community Drug Distributor.
[e]Economic costs include financial costs (monetary transactions) and estimates of the monetary value of goods or services for which no financial transaction has taken place (for example, the opportunity cost of the CDDs' time donated to administer ivermectin rather than working their fields) [18].
doi:10.1371/journal.pntd.0002452.t002

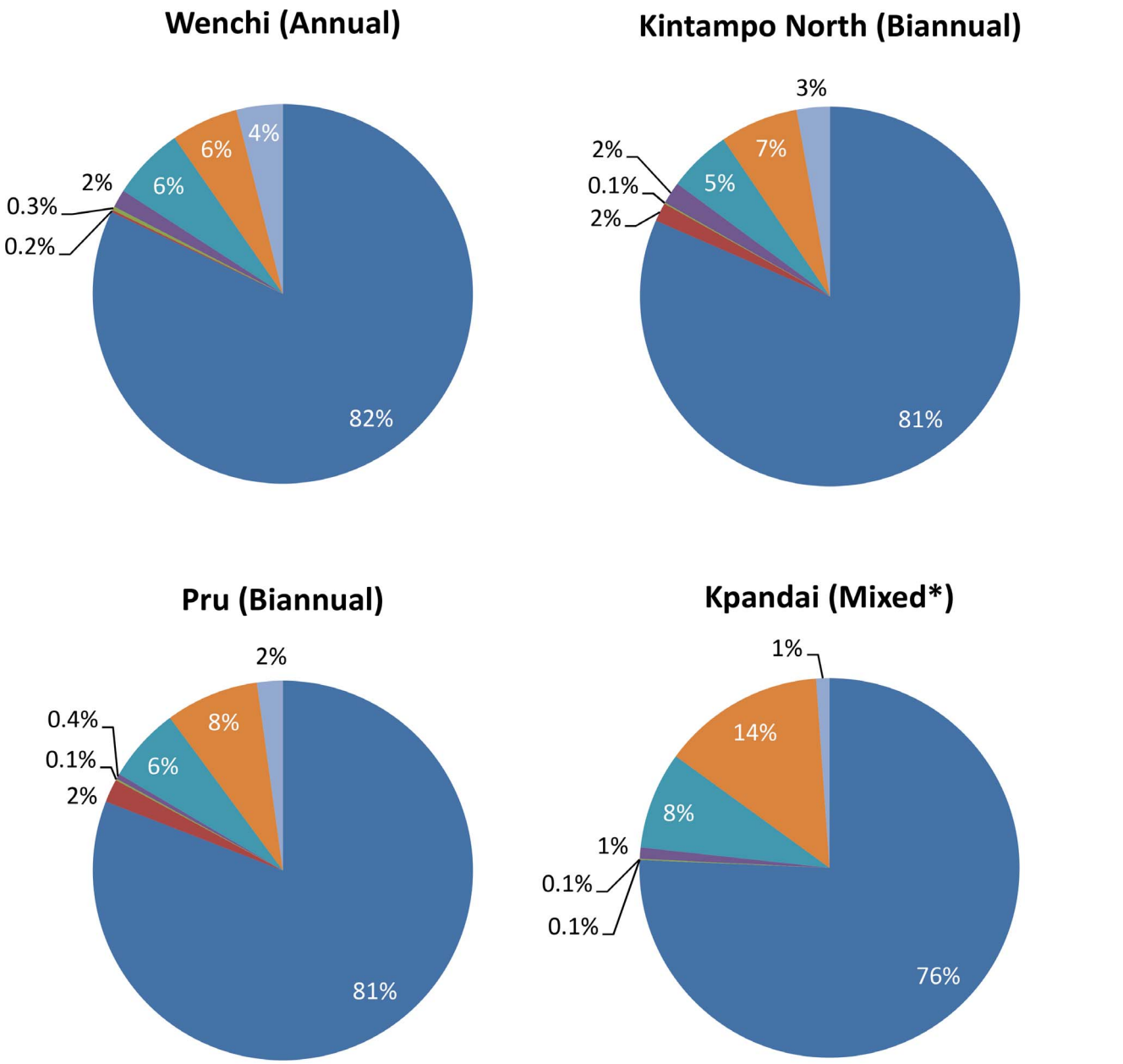

Figure 3. Economic costs at district, sub-district, and community levels disaggregated by resource type (excluding CDDs' time). *Personnel* (dark blue); *Per Diems* (red); *Supplies and Equipment (Capital costs)* (green); *Supplies and Equipment (Recurrent costs)* (purple); *Transportation (Capital costs)* (turquoise blue); *Transportation (Recurrent costs)* (orange); *Overheads* (light blue). Definitions of different resource types are given in Box 2. *Data from Kpandai district reflect a combination of annual and biannual treatments.
doi:10.1371/journal.pntd.0002452.g003

the amount of time they spent on reporting activities (the percentage of the economic cost at the district, sub-district, and community levels attributed to reporting activities increased from 6% in the districts (Wenchi) treated annually to 15% in the districts treated biannually (Pru and Kintampo North) (Figure 4)).

Discussion

The estimated economic cost of annual CDTI in Wenchi district, i.e. USD 0.40 per person per year excluding CDDs' time, is consistent with the lower range of costs reported by McFarland *et al.* [17], who estimated an average economic cost (excluding CDDs' time) of USD 0.62 (2011 prices) per person per year from 10 regions (excluding one region co-endemic with *Loa loa*) across Cameroon, Nigeria and Uganda (with values ranging from USD 0.39 to USD 2.77 (2011 prices)). The estimated cost of annual CDTI presented here is 1.4 times higher than the USD 0.29 (2011 prices) per person estimated by Onwujekwe *et al.* [25] using data from two Nigerian communities. However, the Nigerian study used a smaller sample of only two communities, and did not collect costs from as an extensive range of sources as we did here, or as done by McFarland *et al.* [17]. Katabarwa *et al.* [26] estimated that in districts of a similar population size to Wenchi, the cost per treatment was USD 0.34 (2011 prices) [26]. However, in districts with a larger population (>100,000 inhabitants) the cost fell substantially to USD 0.13 (2011 prices) [26]. These estimates are

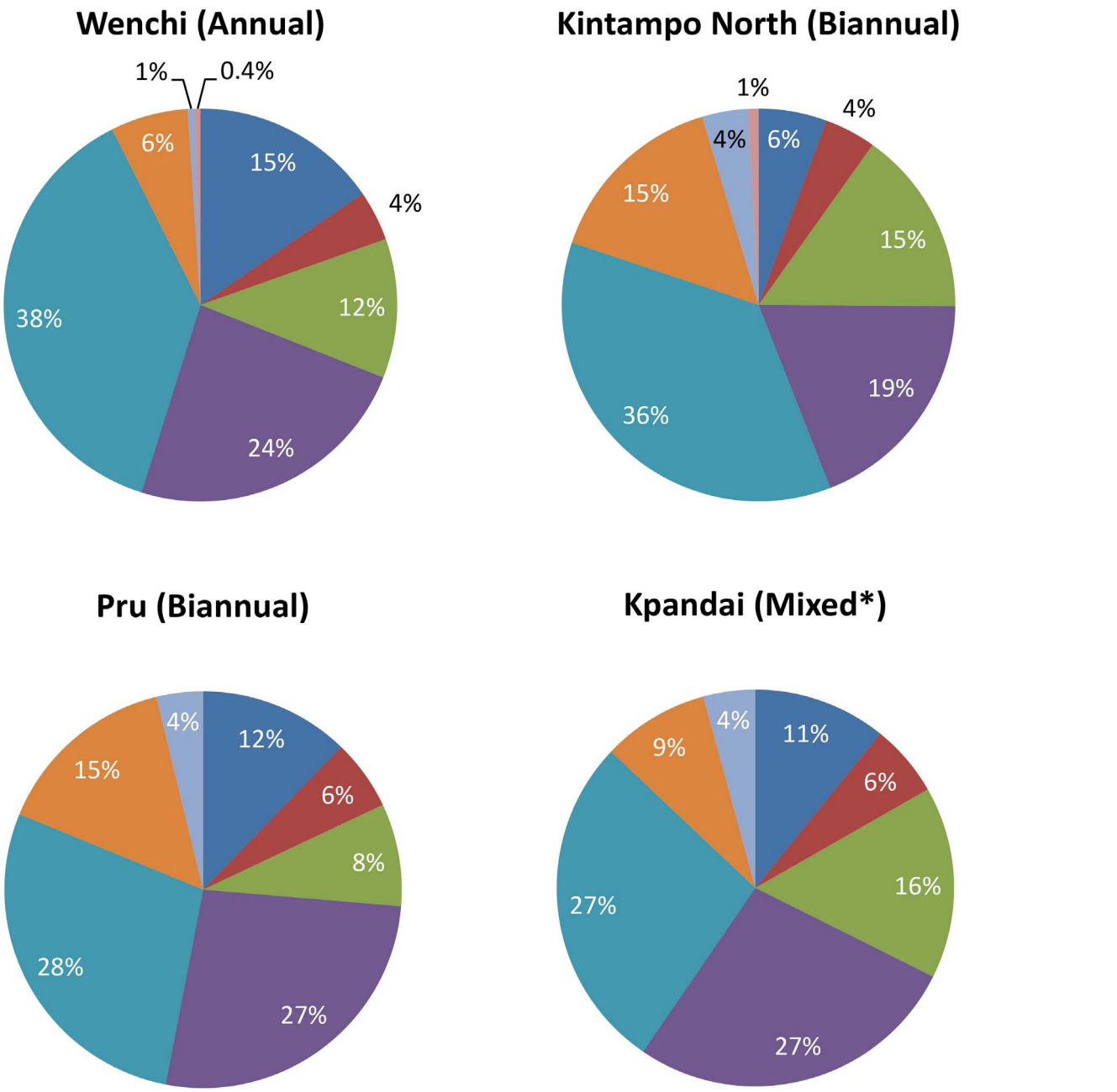

Figure 4. Economic costs at district, sub-district, and community levels disaggregated by programmatic activity (excluding CDDs' time). *Training of Volunteers* (dark blue); *All Other Training* (red); *Mobilization/Sensitization* (green); *Drug Distribution Chain* (purple); *Surveillance and Evaluation* turquoise blue); *Reporting* (orange); *All Other Administration* (light blue); *Other Project Activities* (pink). Definitions of programmatic activities are given in Box 1. *Data from Kpandai district reflect a combination of annual and biannual treatments.
doi:10.1371/journal.pntd.0002452.g004

broadly consistent with the cost of annual mass drug administration (MDA) for lymphatic filariasis control presented by Goldman *et al.* [27], in which the estimated financial cost per treatment (with donated ivermectin and albendazole) in Ghana was USD 0.21 (2011 prices) but varied between USD 0.08 and USD 2.91 (2011 prices) across the whole multi-country study.

The estimated cost of biannual CDTI per person per year in the Pru and Kintampo North districts was 50–60% higher than the estimated cost of annual (in Wenchi) treatment. This is consistent with the estimated increase in costs associated with biannual MDA for lymphatic filariasis control provided by Stolk *et al.* [28] (who estimated for Africa, a 63% increase in the cost of treatment per year excluding the value of donated drugs). These costs are higher than estimates for biannual treatment at smaller scales and specific age groups, such as in school-based anthelmintic treatment programmes. For instance, Phommasack *et al.* [29] found that the annual cost of treatment of soil-transmitted helminthiases in a school-based programme was 35% higher in provinces treating biannually than in those treating annually. However, school-based treatment programmes are implemented differently than community-based programmes and therefore the change in costs of different treatment frequencies cannot be directly compared.

Caution is also advised when comparing the costs of different strategies estimated using data from different districts. This is because districts have different characteristics, such as road conditions, spread of communities, and population densities, which will affect the estimated cost of CDTI. Because of these potential difficulties, study participants in the Pru and Kintampo North districts were asked to estimate—based on their previous experience—the percentage allocated to a given resource had this resource hypothetically been used for an annual treatment strategy. Thus, the estimated hypothetical economic cost (Table 3) of treating annually in the Pru and Kintampo North districts (USD 0.39 and USD 0.43 per person per year, respectively) were consistent with the actual cost estimates of treating annually obtained for Wenchi (USD 0.40 per person per year). This supports the estimated 50–60% increase in costs when treating biannually compared to treating annually. The difficulties associated with comparing fairly costs among districts within Ghana exemplify a more general conundrum of comparing results of health economic analyses conducted in different locations, such as the complexity of comparing data collected from different countries with differently structured economies and healthcare systems, and where public health interventions may comprise different (e.g. school-based versus community-based) modalities of delivery.

Our estimated economic cost of CDTI in the Kpandai district, where both annual and biannual treatments are delivered, likely reflects more closely the cost of annual rather than biannual CDTI since only 15 of 76 (20%) of the communities in the sampled sub-district receive biannual treatment (with the remaining 80% receiving annual CDTI). This possibly explains why the estimated cost per person per year in the Kpandai district was only marginally higher than that in Wenchi (USD 0.43 for the former versus USD 0.40 for the latter), in which only annual treatments are delivered. Furthermore, Kpandai has a very high population density which could reduce the cost per treatment (as found in [26]). Across the whole district, 122 of 222 (55%) of the communities are treated annually and the remaining 45% receive biannual CDTI. Therefore, it is reasonable to expect overall, the actual cost of ivermectin treatment for Kpandai will lie in between the estimated costs of annual and biannual CDTI.

Costs Disaggregated by Resource Type and Programmatic Activity

The costs disaggregated by resource type were consistent among the sampled districts. These data are also similar to those presented by McFarland *et al.* [17]. The recurrent transportation cost was notably higher in Kpandai compared with the other districts. This may in part be due to the poorer quality of roads in the area, resulting in higher vehicle maintenance and fuel costs (although many other factors, including the spread of the communities, also affect transportation costs). The costs disaggregated by programmatic activity showed slightly more variation among districts than among the different resource types. It is noteworthy that in the Pru and Kintampo North districts (and to a lesser extent in the Kpandai district), the percentage of the economic cost attributed to reporting activities at the district, sub-district, and community levels is substantially higher than that in the Wenchi district (15% in Pru and Kintampo North compared to 6% in Wenchi) (Figure 4). This was attributed to the increase in treatment frequency and is discussed in further detail in the section on *Reported Obstacles Associated with Switching from Annual to Biannual CDTI.*

Community Distributors

The compensation system for CDDs has recently been implemented in Ghana to cover their transport costs, to facilitate attendance of training days, and to help serve as an added incentive. The amount received by CDDs per treatment round was corroborated at the district health centres. Generally, the reported amount received by the community distributors was very consistent across communities and districts.

Accounting for the volunteer CDDs' time added approximately USD 0.05 per person per treatment round. The is consistent with the value reported by Onwujekwe *et al.* [25], who found that taking into account volunteer CDD time in two Nigerian communities added approximately USD 0.07 (2011 prices) per person per treatment round (using the Nigerian minimum wage to value the volunteer CDDs' time). However, both our and the Onwujekwe *et al.* [25] estimates are substantially lower than that reported by McFarland *et al.* [17], who estimated that accounting for volunteer CDDs' time added an average of USD 0.19 (2011 prices) per treatment round (valuing volunteer time based on the average per capita Gross National Income (GNI) for each of the three countries studied in [17], namely, Cameroon, Nigeria and Uganda). However, this estimate was highly variable between the different study sites (USD 0.05–0.54 (2011 prices) per treatment round). The use of different methods to value donated CDDs' time (see below) could partly explain the difference (i.e. estimation using the country's minimum wage, or using the country's per capita GNI). Other possible explanations include the occurrence of cultural differences affecting the time it takes to distribute the drug.

As mentioned above, the method used to value the volunteer CDD's time has marked effects on the cost output. For example, we assumed the market value of the volunteer CDD's time to be USD 2.36 per day (the minimum wage in Ghana of GHC 3.73 divided by the 1.58 exchange rate [23]) based on the wage that a farmland worker would receive (i.e. the wage received for the most common alternative occupation) [21,30]). However, had we valued the volunteer CDDs' time using the per capita GNI method (as used by McFarland *et al.* [17]), this figure would have increased to USD 4.96 per day [21,30]. This difference may seem

Table 3. Hypothetical cost (USD) of annual CDTI in Kintampo North and Pru districts, Brong-Ahafo region, Ghana.

Cost Type	Estimated Annual Cost Per Person Treated if Annual Distribution were Implemented	
	Kintampo North	Pru
Financial cost	0.42	0.38
Economic cost (excluding volunteer CDD's time)	0.43	0.39
Economic Cost (including volunteer CDD's time)	0.47	0.44

Abbreviations and cost explanations as in Table 2.
doi:10.1371/journal.pntd.0002452.t003

relatively small but when these costs are factored up to the district level, they can become substantial.

Reported Obstacles Associated with Switching from Annual to Biannual CDTI

Disease control officers at the district health centres reported that increasing the treatment frequency to twice per year increased substantially the amount of time they spent on reporting activities. This is consistent with the costs disaggregated by programmatic activity (Figure 4), which indicate that the time spent on reporting activities increased more than any other project activity when comparing biannual and annual treatments. This may potentially lead to delays in ivermectin being delivered to the districts, if the necessary reports for the next dispatch of drugs are not completed on time (delivery of the next batch of ivermectin being contingent on reporting). Delays in the delivery of treatment to communities not only will have administrative implications, but more importantly, transmission implications. Treating individuals every 6 months is highly important for transmission suppression, as it has been estimated that adult *O. volvulus* female worms start recovering from the temporary sterilising effects of ivermectin approximately between three and four months after treatment, and by six months microfilarial production has recuperated to a substantial degree [31]. Therefore, delays in treatment will permit more transmission, ultimately making the disease harder to eliminate and diminishing the benefit of treating biannually. National onchocerciasis control programmes which consider increasing CDTI frequency may need to support reporting activities at the district level and potentially at the drug donation programme level to encourage timely reporting but also to allow greater flexibility in deadlines to minimize delays in drug distribution.

Data Limitations

In Ghana, onchocerciasis control is under the remit of the NTDP and therefore different disease control programmes are often integrated. For example, onchocerciasis and lymphatic filariasis control activities are often carried out simultaneously. Potentially, this can lead to difficulties in obtaining accurate costs for a single disease intervention. In addition, this study was retrospective, and therefore, to a certain extent, the data obtained were subject to some degree of recall bias.

In order to reduce the time and logistical complexity involved in collecting the cost data, our sampling strategy was not random, as we purposely visited local government offices and communities in districts where CDTI was annual, biannual, or a combination of the two. However, we were only able to obtain data in one district that implements annual treatment and one sub-district in each of the districts. Also, the selected districts may have been more accessible by road from Accra, the capital of Ghana, than other more remote locations. Nonetheless, there is no reason to assume that the costs reported for the sites included in this study (either delivering annual or biannual CDTI) are not representative of other sub-districts in the area, nor is there a treatment cost-associated reason as to why an area switched from annual to biannual CDTI other than the parasitological criteria listed above. This is confirmed by the similarity of cost estimation of annual treatment between the districts delivering only annual CDTI and the sub-districts also delivering yearly treatment within districts implementing both strategies. Due to logistic reasons, the regional level costs in the Northern region were assumed to be the same as those estimated from Brong-Ahafo region. However, due to differences between the regions (such as road networks and community scattering), the costs incurred in the Northern region may be higher. Nevertheless, this assumption will not affect the main conclusions of the study regarding the relative costs of annual vs. biannual treatment.

Concluding Remarks

Our estimate of the cost of annual CDTI is consistent with the range of values previously reported in the literature [17,25,26]. Our results indicate that the cost of biannual ivermectin treatment was approximately 50–60% higher than the cost of annual treatment, and that simply doubling the cost of annual CDTI does not yield a correct estimate as some studies have assumed [11]. This is higher than estimates for increasing treatment frequency obtained at smaller scales and when targeting specific age groups, such as those associated with school-based anthelmintic treatment programmes [29], which are not truly relevant for onchocerciasis, but similar to estimates for the more comparable lymphatic filariasis control programme [28]. Our study will be beneficial in informing economic evaluations regarding cost-effectiveness analyses of increasing CDTI frequency from annual to biannual in the African context for the control and elimination of human onchocerciasis.

Acknowledgments

We thank Dr Justice Nonvignon (University of Ghana) for his valuable comments on the data analysis, as well as Dr Issac Osei-Akoto (Institute of Social, Statistical and Economic Research, University of Ghana). We also thank Dr Jacqueline Leslie (Imperial College London) for useful discussions and Mr Simon O'Hanlon (Imperial College London) for his valuable comments on the data collection and help with the preparation of Figure 1.

Author Contributions

Analyzed the data: HCT. Wrote the paper: HCT MW TSC MGB. Collected the data: HCT MYOA EJT OA NKB. Read and approved the final, submitted version: HCT MYOA MW EJT TSC OA NKB MGB.

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Vaccinating Women Previously Exposed to Human Papillomavirus: A Cost-Effectiveness Analysis of the Bivalent Vaccine

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Abstract

Recent trials have indicated that women with prior exposure to Human papillomavirus (HPV) subtypes 16/18 receive protection against reinfection from the HPV vaccines. However, many of the original models investigating the cost effectiveness of different vaccination strategies for the protection of cervical cancer assumed, based on the trial results at that time, that these women received no protection. We developed a deterministic, dynamic transmission model that incorporates the vaccine-induced protection of women with prior exposure to HPV. The model was used to estimate the cost effectiveness of progressively extending a vaccination programme using the bivalent vaccine to older age groups both with and without protection of women with prior exposure. We did this under a range of assumptions on the level of natural immunity. Our modelling projections indicate that including the protection of women with prior HPV exposure can have a profound effect on the cost effectiveness of vaccinating adults. The impact of this protection is inversely related to the level of natural immunity. Our results indicate that adult vaccination strategies should potentially be reassessed, and that it is important to include the protection of non-naive women previously infected with HPV in future studies. Furthermore, they also highlight the need for a more thorough investigation of this protection.

Citation: Turner HC, Baussano I, Garnett GP (2013) Vaccinating Women Previously Exposed to Human Papillomavirus: A Cost-Effectiveness Analysis of the Bivalent Vaccine. PLoS ONE 8(9): e75552. doi:10.1371/journal.pone.0075552

Editor: Diane Medved Harper, University of Missouri Kansas CIty School of Medicine, United States of America

Received May 11, 2013; **Accepted** August 19, 2013; **Published** September 26, 2013

Funding: Dr. Iacopo Baussano is supported by the following grant sponsors: European Community's Seventh Framework Programme (FP7/2007-2013; acronym PREHDICT), grant number: 242061; and the Bill & Melinda Gates Foundation, grant number: OPP1053353. Geoff P. Garnett acknowledges support from the Wellcome Trust, grant number: 090285/Z/09/Z. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: Geoff Garnett has acted as consultant for and/or received grants for other studies from Sanofi Pasteur MSD, Merck, and GSK. Hugo Turner and Iacopo Baussano have no competing interests. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

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Introduction

Human papillomavirus (HPV) infection is necessary for the development of cervical cancer in women. In the UK, despite a well organised screening programme that achieves high coverage [1], it is estimated that every year 2,890 women are diagnosed with cervical cancer and 1,111 deaths a year are associated with the disease [1]. In addition, HPV has been linked to anal, vulval, vaginal, penile, and oropharyngeal cancers [2]. These cancers would not be detected in the current screening programme. Two high efficacy prophylactic vaccines against HPV have been developed; a bivalent vaccine (CervarixTM) which protects against types 16 and 18, which are responsible for 79% of cervical cancers in the UK [1], and a quadrivalent vaccine (GardasilTM) that also protects against types 6 and 11 (which are associated with anogenital warts).

Since their license, many countries have introduced routine HPV vaccination programmes targeting adolescent girls before sexual debut. Several countries have also implemented catch-up programmes covering older adolescents [3]. For example, in the UK, the Joint Committee on Vaccination and Immunisation recommended a catch-up vaccination programme of girls aged 13 to 17, which started in 2008 [4]. However, though the United States offer HPV vaccination to women up to 26 years of age [5], few countries have offered HPV vaccination to older age groups, and the uptake for the catch-up programmes has been generally low [6,7].

Due to the complexity of HPV transmission and natural history of cervical cancer, as well as the long delay between infection and clinical outcomes, mathematical models are needed to predict the long-term benefits of different vaccination strategies. Many of the older HPV models made the

assumption (based on the trial results at that time) that the vaccine only offers protection to women who had not been previously infected (i.e. are naive to infection) [8,9,10,11,12]. However, when the analysis of the phase three bivalent vaccine trial was expanded to include women that were not currently infected but who had previous serological exposure to HPV 16/18 infection (i.e. women who are non-naïve to infection), it was found that the vaccine had a comparably high efficacy in this group of women as the HPV naive women [13]. Similar trial results have also been reported for the quadrivalent vaccine [14]. This is important as the results from models that do not include vaccine protection in non-naive women may underestimate the cost effectiveness of including older age groups in catch-up programmes. This has implications for policy decisions on which age groups should be included in vaccination strategies.

Although many models have since included this protection to non-naive women [15,16,17,18], to the best of our knowledge no other model has been devised to explicitly investigate the benefit of this protection and the implications it has on the cost effectiveness of vaccinating adults using a dynamic transmission model.

We constructed a model that quantifies the potential protection of women with prior exposure to HPV16/18 to investigate the effect of this protection on the cost effectiveness of extending the vaccination catch-up programme to older age groups in the UK. In addition, we explored a range of lower vaccine costs than in previous economic analyses [15], to reflect that the government negotiated vaccine price will likely be lower than the list price assumed in many economic evaluations.

Materials and Methods

Model procedures

We developed a deterministic, dynamic transmission model to represent acquisition and heterosexual transmission of infection, with an embedded progression model to represent the subsequent development of HPV-related disease. The model, partly based on Jit et al. [15] was stratified by HPV type, age, gender and sexual activity based risk group. More detail is provided in the File S1.

HPV types in the model were divided into four groups: type 16, type 18, other oncogenic high-risk types with vaccine cross protection and other oncogenic high risk types without vaccine cross protection. We used type specific model compartments to represent women being susceptible to HPV infection, infected with HPV or immune to infection. The susceptible compartments were further subdivided into naive and non-naive to HPV infection. Non-naive women (i.e. women with prior exposure to HPV) were assumed to occupy the susceptible non-naive or naturally immune compartments. The type-specific infected compartments in women were subdivided into being infectious but free of disease, having cervical intraepithelial neoplasias of different grades (CIN I, II, or III), and having invasive squamous cell carcinoma (SCC). We adopted the same structure for adenocarcinomas, with states for cervical glandular intraepithelial neoplasia (CGIN) replacing CIN. A specific precursor lesion state could regress to a less severe state, to the immune state, or to susceptible (non-naive) state, either as a result of natural regression (at rates independent of age) or age-dependent screening and treatment (see Tables S4 and S5 in File S1 for progression/regression and screening rates). Men were assumed only to occupy type-specific model compartments representing HPV susceptible, infected and immune.

The model population consisted of individuals aged between 12 and 74 years old, divided into 10 age classes based on data from the Office of National Statistics [19]. The model population was stratified into three sexual behaviour groups. More detail is provided in Table S2 in File S1.

Parameter estimation

Using nonlinear least-squares regression the model was fitted to HPV type and age-specific prevalence data [20], by estimating a type-specific transmission probability (See File S1for details). If women were found to be infected with multiple types of HPV in the data, we assumed women to have the most oncogenic HPV type(s) present when fitting the model (i.e. if the data showed a woman was positive to both HPV16 and 18, that person was classified as HPV16 in the model). By estimating the age dependent and HPV type specific progression rate of CIN III to SCC and CGIN III to adenocarcinomas, the model's predicted cancer incidence was fitted to data on the number of cancer cases reported in the UK and to data describing the distribution of HPV types in cancer cases [21,22]. Double counting of disease outcomes was avoided by attributing cancer to the most oncogenic HPV type(s) present. Due to the lack of knowledge of immunity against HPV, we repeated our model simulations under different assumptions of the level of natural immunity (described in the sensitivity analysis section). The model was refitted for each different natural immunity scenario i.e. for each different immunity assumption we had a different transmission probability and a different cancer progression rate to ensure that the incidence of cancer matched the observed data in all of the scenarios we investigated. The range of parameter values estimated is shown in Table S8 in File S1.

Vaccination

The model assumed the vaccine gives naive women 100% protection against HPV16/18 infections [23]. In addition, the model assumed that the vaccine has cross protection to the high risk HPV types not included in the vaccine (with a 47% efficacy against infection) based on clinical trial data for the bivalent vaccine [24], and other modelling studies [17]. To quantify the effect of the protection of women non-naive to HPV16/18, we varied their protective vaccine efficacy against infection between 0% and 100%. It was assumed a woman would need at least two doses of the vaccine to receive any protection [25]. For catch-up campaigns, women aged over 16 years were assumed to receive their vaccination through general practice clinics. Dose specific coverage estimates of each age class were matched to reported annual HPV vaccine coverage data (See Table S6 in File S1). All three doses of the vaccine were assumed to be given in the same year [26].

Vaccine-induced protection may wane moving vaccinated individuals to a susceptible (non-naive) compartment. The duration of vaccine protection, which was varied as part of the sensitivity analysis was assumed to be the same for both naive and non-naive women. The vaccine is assumed to offer no benefit to women who are currently infected with HPV providing no effect on an individual's lesion status and no effect on the rate of HPV clearance [27,28]. The vaccine is assumed to have no effect on non-naive individuals' risks to other high-risk HPV types.

Cost effectiveness analysis

We analysed the cost effectiveness of a range of vaccination strategies using a healthcare provider perspective. The baseline scenario was the current UK vaccination programme, i.e. vaccination of girls aged 12-13 using a school based programme and with a catch-up programme of 14-17 year olds as well as screening and treatment of older women (based on the current UK screening programme - see File S1 for details). We investigated a range of other vaccination strategies by varying the age of catch up. We did not explore vaccination programmes targeting adolescent males.

We measured the incremental cost effectiveness ratio (cost per Quality Adjusted Life Year (QALY) gained) of progressively extending the catch-up programme to older age groups, over a 100 year time horizon. This was calculated by dividing the additional cost by the additional benefit of a particular vaccination programme compared to the previous vaccination strategy i.e. the next most expensive option. Our baseline scenario was compared to a programme using screening and treatment only. The unit of effectiveness was QALY gained (details provided in File S1). This analysis used a willingness to pay threshold of £30,000 per QALY gained, which is the standard cut-off value usually used by the National Institute for Health and Clinical Excellence for evaluating health technologies in the UK [29]. See Table 1 for the parameter values for the cost and utility weights. Following the National Institute for Health and Clinical Excellence guidelines, the costs and the benefits were discounted at 3.5% at baseline and the discount rate varied as part of the sensitivity analysis [30].

Sensitivity analysis

In order to investigate the effect of the protection of women non-naive to HPV, we varied their vaccine efficacy between 0% and 100%. To reflect the uncertainty surrounding the natural history of the infection, we performed a multi-way sensitivity analysis on the level of natural immunity; both the proportion that experience immunity (25%, 50%, 75%, and 100%), and the duration of immunity (2 years, 10 years, 20 years, and lifelong) were varied. These simulations were summarised as median values with an interquartile range (IQR) to illustrate the variations in the potential cost-effectiveness of the vaccine depending on the level of natural immunity. Because there is no data providing an estimate of the duration of vaccine induced immunity, we present a set of scenarios with different durations of vaccine- associated immunity (10 years, 20 years, and lifelong). Because the UK government purchased the Cervarix vaccine from GlaxoSmithKline at a negotiated and undisclosed price, we also varied the cost of each vaccine dose (£20 and £40 per dose not including the costs of administering the vaccination, which are described in Table 1and File S1). This assumes that the negotiated price is much lower than the listed price of £80.50 per dose [38]. The discount rate was varied between 0% and 6% [30]. In addition the sensitivity of the results to the assumed vaccination coverage of 12-13 year old school girls was investigated.

Table 1. Parameters used in economic model.

Health State	Utility
CIN I	0.91 [31]
CIN II	0.87 [31]
CIN III	0.87[31]
Cancer	0.6* [32]
Cancer Treatment	0.84* [32]
Positive pap smear result received	0.98 [31]
Screening and Treatment	**Costs**
Cost per Screening (Pap Smear)	£29.02 [33]
Colposcopy	£173.58[34]
Treatment of precancerous lesions	£383.63[34]
Treatment of cancer	£20231.33* [34,35]
Vaccine	**Costs**
Cost per dose	£40 or £20 (estimates)
Administration cost per dose (School based)	£5.30[36]
Administration cost per dose (GP based)	£11.87 [37]

* indicates that the parameters are a weighted average of the four different Federations of Gynecologists & Obstetrician stages.

CIN: cervical intraepithelial neoplasias. CGIN: cervical glandular intraepithelial neoplasia. Prices are adjusted to 2011.

doi: 10.1371/journal.pone.0075552.t001

Results

On the basis of our model output's 'goodness of fit' to HPV prevalence data [20], we included 75% of our natural immunity scenarios in our cost effectiveness analysis. The scenarios that we excluded (based on their root-mean-square deviation) notably underestimated HPV16 prevalence, and therefore would have underestimated the vaccine's impact (see File S1). Table 2 shows the estimated costs that would be incurred and the potential QALYs gained over a 100-year period after the introduction of the vaccine (the results were averaged across the estimates obtained for the different assumptions regarding the level of natural immunity (which is unknown)). The incremental cost of extending the vaccine programme increased with the inclusion of older age groups (see Table 2). However it should be noted that the true incremental cost of extending the vaccine programme will be highly depended on the cost of the vaccine. The vaccination programme generated some cost savings to the health service (approximately £336 million for the current UK strategy) by reducing the number of treatments (for precancerous lesions and cervical cancers), but these savings were outweighed by the cost of the vaccination programme itself.

Table 2. Discounted additional costs

Incremental QALYs gained:				
Vaccination Programme:	**Mean incremental QALYs gained (total)**	**Mean incremental QALYs gained due to cancers prevented**	**Mean incremental QALYs gained due to reduced treatment**	**Median incremental QALYs**
Ages 12-17	88,392*	52,313*	36,079*	90,108 (77,904-95,175)*
Ages 12-19	4,103†	2,428†	1,675†	4,424 (3,980-8765) †
Ages 12-24	7,979†	4,722†	3,257†	8,318 (7,750-10,049) †
Ages 12-29	4,927†	2,916†	2,011†	5532 (5,169-6,623) †
Ages 12-34	3,334†	1,973†	1,361†	3,347 (3,101-4,136) †
Incremental cost:				
Vaccination Programme:	**Mean incremental cost of programme**	**Mean incremental net cost**	**Mean incremental cost saved**	**Median incremental net cost**
Ages 12-17	£884*	£538*	£336*	£523 (514-565) *
Ages 12-19	£76†	£57†	£19†	£55 (54-57) †
Ages 12-24	£180†	£145†	£35†	£144 (142-148) †
Ages 12-29	£176†	£162†	£14†	£160 (158-163) †
Ages 12-34	£174†	£172†	£2†	£172 (168-174) †

The vaccine was assumed to cost £20 per dose, last an average of 20 years and provide protection to women with previous exposure to HPV (100% efficacy). The median and mean results are averaged across the estimates for different assumptions of natural immunity (the 1st and 3rd quartiles are shown in brackets). All programmes assume routine vaccine of 12-13 year old girls. *QALY: Quality adjusted life year.*

* Costs or benefits compared to a programme only using screening and treatment

† Costs or benefits compared to the previous vaccination option i.e the next most expensive option

doi: 10.1371/journal.pone.0075552.t002

The effect of including the protection of non-naive women on the cost effectiveness of vaccinating 12-13 years olds was negligible. However, it substantially increased the cost effectiveness of vaccinating older women in catch-up programmes. The outcome of the cost effectiveness analysis was also highly dependent on the price of the vaccine and the average duration of protection provided by the vaccine. The level of natural immunity was also found to be inversely related to the cost effectiveness of vaccination, with the higher the level of natural immunity the lower the cost effectiveness of vaccination. The variation in the incremental cost effectiveness ratios caused by the different natural immunity assumptions increased with the age of the group being vaccinated (the median results averaged across the estimates for different assumptions of natural immunity are shown in Table 3). In addition, when higher levels of natural immunity are assumed, the protection of non-naive women has a lower beneficial impact on the cost effectiveness of the vaccine.

When assuming the presence of protection to non-naive women, the majority of simulations for extending the vaccine programme to include 18 and 19 year olds were cost effective (using a threshold of £30,000 per QALY gained). This extension strategy was not found to be cost effective in the absence of protection to non-naive women, if the cost per dose was £40. The cost effectiveness acceptability curves for extending the catch-up programme to 19 year olds are shown in Figure 1A.

Furthermore, when assuming the vaccine provides 20 years of protection and a cost per dose of £20, extending the catch-up programme further to include 20-24 year olds was found to be cost effective (£22,286 per QALY gained) in the presence of protection to non-naive women. However, this was not cost effective in the absence of the protection to non-naive women (£39,849 per QALY gained). In addition, when the vaccine was assumed to provide both lifelong protection and protection to non-naive women, the results for this strategy were highly cost effective if the vaccine costs £20 per dose (£16,557 per QALY gained), and borderline cost effective if the vaccine costs £40 per dose (£29,021 per QALY gained). However, in the absence of the protection to non-naive women the cost effectiveness decreased substantially (£34,839 and £62,011 per QALY gained respectively). The cost effectiveness acceptability curves for extending the catch-up programme to 25 year olds are shown in Figure 1B. Strategies targeting women over 25 were only found to be borderline cost effective with a vaccine cost of £20 per dose and assuming the vaccine provided both lifelong protection and full protection to non-naive women.

When assuming a lower coverage of the school based programme (targeting 12-13 year olds), the cost effectiveness of extending the vaccine programme to include older women notable increased (see Figure S4 in File S1).

Discussion

Our economic analysis indicates that the effect of including the protection of women non-naive to HPV on the cost effectiveness of vaccination of 12-13 years is negligible (likely due to the low number of women that have experienced infection in this age group). However, this protective effect can have a substantial effect on the outcome of the cost effectiveness of vaccinating older women in catch up programmes. This was particularly evident in 18-25 year olds, who are not often included in vaccination programmes in Europe [3]. It is worth noting that the impact of including vaccine protection to non-naive women on the vaccine's cost-effectiveness ratios is affected by the level of natural immunity in the population (with lower benefits if a higher level of natural immunity is assumed). This should be considered in future modelling studies incorporating this protection. When assuming the vaccine provides protection to non- naive women, we assumed that efficacy against infection was the same as that for naive women (i.e. 100%), which may be an overestimate [13]. We therefore varied the efficacy in non-naive women as part of our sensitivity analyses and found that even with a lower

Table 3. The median incremental cost effectiveness ratios of alternative vaccination catch-up programmes.

£20 per dose		
	Protection to non-naive women	**Absence of protection to non-naive women**
Vaccination Programme:	**Median (IQR)**	**Median (IQR)**
20 years' vaccine protection:		
Ages 12-17 (Current)	**£4,089 (3,981-5,910)***	**£4,101(4,027-5,774)***
Ages 12-19	**£14,691 (12,820-20,047)** †	**£20,380 (17,999-29,587)** †
Ages 12-24	**£22,286 (19,093-36,929)** †	£39,849 (35,691-55,984) †
Ages 12-29	£51,816 (41,723-74,516) †	£116,327 (106,273-147,262) †
Ages 12-34	£103,156 (77,921-159,226) †	£335,481 (311,499-406,802) †
Lifetime vaccine protection:		
Ages 12-17 (Current)	**£1,627 (1,525-1,922)***	**£1,801 (1,714-2,001)***
Ages 12-19	**£10,433 (9,110-12,455)** †	**£16,769 (14,533-20,947)** †
Ages 12-24	**£16,557 (14,126-17,852)** †	£34,839 (30,060-42,360) †
Ages 12-29	£33,897 (30,850-36,915) †	£105,637 (90,244-118,537) †
Ages 12-34	£50,125 (39,723-58,561) †	£254,191 (200,629-324,487) †
£40 per dose	**Protection to non-naive women**	**Absence of protection to non-naive women**
Vaccination Programme:	**Median (IQR)**	**Median (IQR)**
20 years' vaccine protection:		
Ages 12-17 (Current)	**£9,476 (8,145-13,357)***	**£9689 (8315-13521)***
Ages 12-19	**£22,268 (17,152-33,507)** †	£38210 (33854-52774) †
Ages 12-24	£36,578 (31,321-60,042) †	£70523 (63236-96679) †
Ages 12-29	£90,320 (73,986-128,491) †	£197865 (180770-249516) †
Ages 12-34	£162,040 (124,938-224,179) †	£563025 (522743-682016) †
Lifetime vaccine protection:		
Ages 12-17 (Current)	**£3,675 (3,317-4,694)***	**£3,802 (3,452-4,856)***
Ages 12-19	**£21,623 (18,404-25,006)** †	**£32,078 (27,300-38,695)** †
Ages 12-24	**£29,021 (27,203-33,887)** †	£62,011 (53,133-74,739) †
Ages 12-29	£60,394 (55,569-66,138) †	£179,880 (153,387-201,579) †
Ages 12-34	£80,278 (65,898-105,678) †	£553,911 (473,101-531,305) †

The incremental cost effectiveness ratios in the presence and absence of protection to non-naive women are shown. No strategies were dominated or extendedly dominated. The median results averaged across the estimates for different assumptions of natural immunity are presented (the 1st and 3rd quartiles are shown in brackets). The costs and benefits have been discounted at 3.5% a year. All programmes assume routine vaccine of 12 year old girls. Median results under the £ 30,000 threshold are shown in bold.

IQR: Interquartile range.

* Cost effectiveness of particular option compared to a programme only using screening and treatment.

† Ratio of additional costs and benefits of particular vaccination programme compared with previous option i.e the next most expensive option.

doi: 10.1371/journal.pone.0075552.t003

value of 50% efficacy, the protection of non-naive women still had a substantial benefit on the cost effectiveness of vaccinating adults (see Figures S5 and S6 in File S1). However, it should be noted that further investigation of this protection and how it may differ from that experienced by HPV naive women is essential.

Our estimates of the cost effectiveness ratios of vaccinating over 18 year olds were substantially lower than those found by the model which informed the UK vaccination strategy, which also took into account this protection to non-naive women [15]. This may be due to the fact that we assumed a lower (estimated) government negotiated price for the vaccine (rather than the vaccine list price of £80.50 per dose) [38]. A study by Bogaards et al. (2011) found that including vaccine protection of non-naive women did not have much bearing on the cost-effectiveness analysis [18]. However, a possible reason for this difference is that their assumptions of vaccine efficacy were only tested as part of a univariate sensitivity analysis, and therefore the effect the level natural immunity has on the projected additional benefits of including the protection of non-naive women were not accounted for [18]. In addition, the study did not account for the effect the increased vaccine protection of non-naive women would have on herd immunity [18].

One of the key strengths of this analysis is that we performed a variety of different simulations, both with and without protection of non-naive women, allowing the additional benefit to be quantified. In addition, dose specific coverage estimates of each age class were matched to reported UK annual HPV vaccine coverage data, capturing the increased dropout rate of the age groups included in the current catch-up programme [6]. However, it should be noted that it is possible that the dropout rate might increase for women aged >18, which requires further investigation. In addition there were some limitations to our approach. We modelled the progression and transmission of each HPV type using separate models (using the method described by [39]). When using separate models, the progression of multiple typed lesions are attributed to the most oncogenic HPV types and this can potentially cause some lesions to be misattributed to the wrong HPV type. However it is not currently possible to accurately parameterize a model for each of the high risk HPV types not included in the vaccine. Although further investigation and quantification of the vaccines impact on other HPV related cancers is important, due to the uncertainties inherent to the progression from HPV infections to these cancers and the lack of available data, we did not incorporate them into our model (therefore the overall health impact from vaccination may be underestimated). Additionally, the model assumed that CGIN lesions were not detected by screening, but in practice some can be detected [40]. Furthermore we did not investigate possible strategies involving vaccinating male adolescents, which though are not used in the UK, are currently being used in Austria and the USA [41]. Based on data reported by Kreimer et al. [25], it was assumed that two doses of the vaccine provide full protection. However it is currently unknown how the number of doses received relates to the duration of vaccine derived immunity (and how much protection is gained by only receiving one dose). More data to inform these parameters in models will be

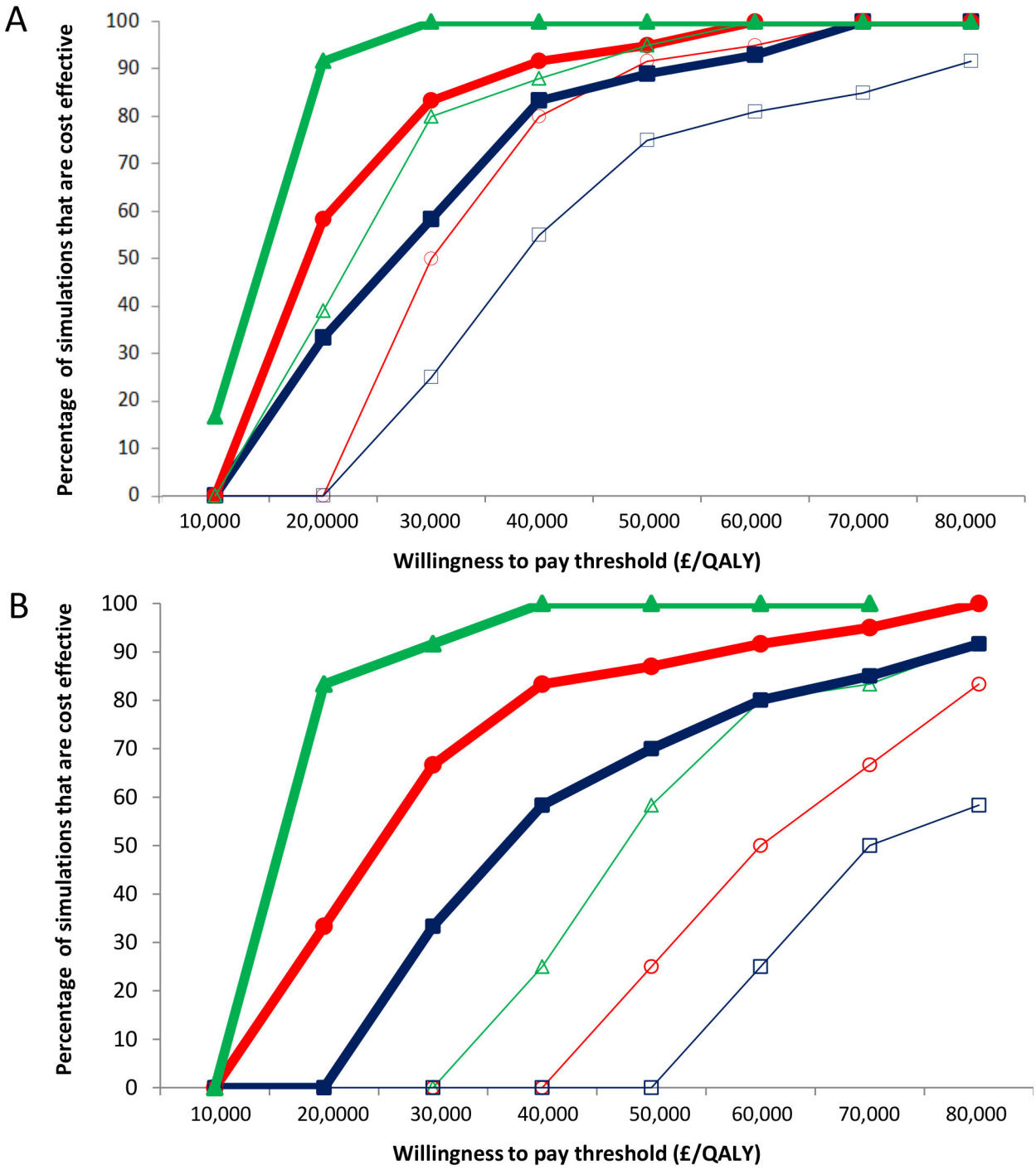

Figure 1. Cost Effectiveness Acceptability Curves for Extending the Vaccination Catch-up to (A) 19 year olds and (B) 24 year olds. Different durations of vaccine induced immunity; Life (Δ), 20 years (○), 10 years (□). Thick lines represent presence of protection to HPV non-naive women and thin the absence. The results presented assumed the vaccine cost is £20 per dose (not including the cost of administering the vaccine) a 100 year time horizon and 3.5% discount rate for costs and benefits. QALY: Quality adjusted life year.

doi: 10.1371/journal.pone.0075552.g001

essential for more accurate estimates of the cost effectiveness of different control strategies. Unfortunately the exact price of the vaccine in the UK has not been disclosed publicly. We assume the vaccine price that the government negotiated is lower than the list price of £80.50 per dose [38]. However it is possible that the negotiated price is higher that estimated. It should be noted that an alternative possibility, not accounted for in the model, is that a specific biological factor modulates the capacity of some women to repeatedly clear an infection, which would affect the added benefit of the protection of non-naive women. Furthermore we assumed that the duration of vaccine and natural derived immunity were independent of each other, though it is possible that vaccination may boost the duration of natural immunity. However, there is currently insufficient data to accurately parameterize such features in an HPV transmission model.

The results of this study indicate that the protection of women non-naive to HPV provided by the vaccine has a substantial effect on the cost effectiveness of HPV vaccination catch-up programmes. This was particularly evident in 18-25 year olds for which the results indicate that if the negotiated vaccine cost is below £40 per dose it may be cost effective to extend the UK's catch-up programme (when assuming comparably high vaccine efficacy in HPV non-naive and naive women). This suggests that if the price of the vaccine is less than £40 per dose, the Department of Health in the UK should reconsider either extending the current catch-up programme or providing a subsidy reducing the cost of private vaccination for women aged 18 to 25. In addition we found that the cost effectiveness of extending the vaccine programme to include older women notably increased when assuming a lower achieved coverage of 12-13 year olds in the school based programmes. This highlights the potential value of this strategy in areas which are currently only attaining a low coverage. However, it should be noted that it is plausible that extending catch-up vaccination to older age groups may lead to women delaying vaccination and this would require further investigation. In addition it is important to consider that offering vaccination to older age groups could potentially lead to a stigmatisation of the school based vaccination programmes (people might believe that only girls that are "planning on their sexual debut" would have the vaccine, potentially decreasing the achieved coverage). In late 2012, the UK's Department of Health switched to the quadrivalent vaccine, which also includes protection against HPV 6/11 (linked to anogenital warts) [42]. A detailed modelling comparison of the cost effectiveness of the two vaccines is presented in Jit et al. (2011) [17]. However, even though our study was based on the bivalent vaccine and on the UK screening programme (so our cost effectiveness estimates may not be directly generalizable to other counties with different screening and vaccine programmes) it still highlights the importance of both how this protection of non-naive women (which has been found for both vaccines) and how lower government negotiated vaccine prices, may affect the cost effectiveness of vaccinating adult women.

Our modelling projections indicate that the protection of non-naive women can have a profound effect on the outcomes of a cost effectiveness analysis of vaccinating adults. This indicates that adult vaccination strategies should potentially be reassessed and demonstrates the importance of including the protection of non-naive individuals in future studies investigating different HPV vaccination strategies such as male vaccination. In addition, this highlights the need for a more thorough investigation of this protection.

Supporting Information

File S1. Model Description and Supplementary Results. Table S1, Parameter definitions. Table S2, Number of new partnerships per year stratified by age and risk group. Table S3, Population size and death rates stratified by age group. Table S4, Screening and treatment rates stratified by age group and neoplastic status. Table S5, Lesion specific progression and regression parameters. Table S6, Vaccination Coverage for each dose stratified by age. Table S7, Effect of altering discount rate on median incremental cost effectiveness ratio. Table S8, HPV type specific incidence and transmission probability. Figure S1, A Flow Diagram of the Model. Figure S2, The differential equations of the model. Figure S3, Model estimates of age specific prevalence of HPV-16 compared to trial data to which it was fitted. Figure S4, Cost effectiveness acceptability curves for extending the vaccination catch-up programme up to 24 year olds (assuming a lower coverage of the school based programme targeting 12-13 year olds). Figure S5, Cost effectiveness acceptability curves for extending the vaccination catch-up programme up to 24 year olds (assuming 75% vaccine efficacy for non-naive women). Figure S6, Cost effectiveness acceptability curves for extending the vaccination catch-up programme up to 24 year olds (assuming 50% vaccine efficacy for non-naive women).
(DOC)

Acknowledgements

We would like to thank Dr Zara Shubber, Dr Isobel M Blake, Ms Véronique Chabanis and Ms Sarah-Jane Anderson for their comments and feedback during the manuscript preparation. Dr Iacopo Baussano is on leave from the University of Piemonte Orientale, Novara, Italy.

Author Contributions

Wrote the manuscript: HT. Designed the study and model: HT IB GG. Carried out the computer simulations and analysis: HT. Drafted the manuscript: HT IB GG. Approved the final version to be published: HT IB GG..

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Imperial College London

Increasing river blindness treatment to twice a year doesn't double cost

by *Sam Wong*
19 September 2013

Ivermectin tablets © Kate Holt/Sightsavers

Distributing treatments for river blindness twice a year instead of annually doesn't double the cost, according to a study in Ghana.

Currently, many African countries give out ivermectin treatment once a year to control the disease, which causes irreversible loss of vision and unbearable itching.

Many countries are now considering biannual treatment in a drive to eliminate river blindness, but until now little data has been available on the cost of adopting this strategy.

The London Declaration on Neglected Tropical Diseases (NTDs), a commitment made by global health organisations and pharmaceutical companies in January 2012, set a target of eliminating river blindness in selected countries in Africa by 2020. The goal was inspired and endorsed by the World Health Organization's 2020 Roadmap on NTDs.

Researchers from Imperial College London, the Council for Scientific and Industrial Research of Ghana, and the Neglected Tropical Diseases Programme of the Ghana Health Service conducted a study to assess the cost of biannual ivermectin distribution in Ghana. They also assessed some of the factors that may hinder the scaling up of treatment frequency at a large scale.

The results, published in *PLOS Neglected Tropical Diseases*, show that the yearly cost of biannual ivermectin treatment is only 50 to 60 per cent higher than that of annual treatment, rather than twice as much, as other programmes have assumed. In addition, large-scale mass biannual treatment was reported as being well received by communities and health workers, and considered sustainable in the context of the Ghanaian NTD control programme.

Hugo Turner, from the School of Public Health at Imperial College London, who led the study, said: "The results of this study will help to inform decisions about whether to increase treatment frequency from annual to biannual for the control and elimination of river blindness in Africa."

River blindness, also called onchocerciasis, is caused by parasitic worms that predominantly affect rural populations who live near fast-flowing rivers in sub-Saharan Africa.

Regular and prolonged treatment with ivermectin can contribute to both reducing the disease burden and the occurrence of new infections..

Following successful control of the disease in some west African countries, the African Programme for Onchocerciasis Control recently introduced a new policy aiming to eliminate the infection where possible in addition to its previous goal of preventing the disease caused by the parasite.

Some countries, such as Ghana and Uganda have already started distributing ivermectin twice per year in some areas. The Carter

Center will oversee the implementation of biannual distribution in parts of Ethiopia where treatment has never been deployed.

“Accurate cost data are essential to inform economic evaluations and policy decisions regarding the implementation of a biannual ivermectin distribution strategy in Africa,” Mr Turner said.

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Reporter

Sam Wong
Communications and Public Affairs

TAGS: neglected tropical diseases

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Costing Questionnaire

Region: |_____|

District: |_____|

Date

What is your position?

How much of your time is spent on onchocerciasis control activates (percentage of the year)?

What is your salary?

Do you receive any additional supplements (such as travel or per Diem)?

What percentage of your time working on onchocerciasis is spent on the following activates:- SEE LAST PAGE

How many people work in this health centre?

How many of these people are associated with onchocerciasis control activates?

Personnel:

Name	Position	Percentage of work time dedicated to onchocerciasis control*	What is their salary?	Additional supplements*

*Indicated how this might have changed since switching to biannual treatment

Supplies and equipment (capital costs):

Input	Number of units	Purchase price	Value (if donated)	Expected useful life	% used on onchocerciasis control activities*

* Indicated how this might have changed since biannual treatment

Supplies and equipment (recurrent costs):

Input	Total annual cost	% used on onchocerciasis control activities *

* Indicated how this might have changed since biannual treatment

Transportation (capital costs):

Input *	Quantity *	Purchase price	Value (if donated)	Expected useful life	% used on onchocerciasis control activities *

* Indicated how this might have changed since biannual treatment

Transportation (recurrent costs):

Input*	Quantity*	Fuel cost (per litre)	Insurance (average per item cost)	Maintenance and repairs (average per item cost)	Taxes, fees, etc. (average per item cost)	% used on onchocerciasis control activities *
If rental vehicle, no. of days (dates) *				**Cost of daily rental**		

* Indicated how this might have changed since biannual treatment

Overheads:

Is any space donated or rented for onchocerciasis control programme activities.				
If donated what would it cost to rent the space?				
Facility (date)	**Building maintenance (per year)**	**Water (per year)**	**Phone (per year)**	**Electricity (per year)**

Are there any other costs not included above
Who gives you the money for the above activates
Have there been any issues caused increasing the treatment frequency to twice a year:

Percentage each input is used on different programmatic activities:

Input	Training Volunteers	Other Training	Mobilization/ Sensitization	Drug Distribution Chain	Surveillance / Evaluation	Reporting	All Other Administration	Other Project Activities