The Health Impact of Onchocerciasis Control in Africa

Luc E. Coffeng

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The Health Impact of Onchocerciasis Control in Africa

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onchocerciasis bestrijding in Afrika

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Introduction to onchocerciasis

The life cycle of the parasite

Onchocerciasis is a tropical disease endemic to Sub-Saharan Africa, Yemen, and parts of Latin America, and is caused by the filarial nematode *Onchocerca volvulus*, which is found exclusively in humans. Adult specimens of this roundworm reside in subcutaneous and deep-tissue nodules, and have an estimated average reproductive life span of about ten years (Duke 1968; Plaisier et al. 1991b). While female worms grow up to 50 cm long and remain sedentary in the nodules, male worms are somewhat smaller (up to 42 cm) and migrate from nodule to nodule, inseminating female worms (Schulz-Key and Albiez 1977; Duke 1993). As long as they are regularly inseminated, female worms produce larvae, so-called microfilariae (mf), which measure up to 360 µm and migrate through the host's tissues and live up to two years (Duke 1968). Mf may be picked up from the host's skin by the bite of a blackfly (genus *Simulium*). In Africa, species of the *S. damnosum* complex are mainly responsible for transmission of infection, whereas in Latin America, several other *Simulium* species drive transmission (Basáñez, Churcher, and Grillet 2009; Adler, Cheke, and Post 2010). All *Simulium* species breed in oxygen-rich water (e.g. river rapids). During their passage through a blackfly, the mf—now called stage L1 larvae—develop and moult into infective stage L3 larvae, which may be transmitted to another human during a fly's next bloodmeal (Duke, Moore, and De León 1967). A small fraction of the transmitted stage L3 larvae eventually develop into adult worms (male or female). In turn, these may start reproducing after a prepatent period of 12 to 16 months (Duke 1968, 1980), completing the cycle of transmission (Figure 1.1).

Clinical symptoms

Onchocercal disease consists of a wide spectrum of eye and skin symptoms. Ocular lesions are caused by the host immune response to parasite antigens and endosymbiotic *Wolbachia* bacteria released at the death of ocular mf (Pearlman and Gillette-Ferguson 2007). Lesions usually occur in both eyes, and range from reversible punctate corneal opacities to irreversible corneal scarring (Figure 1.2f)

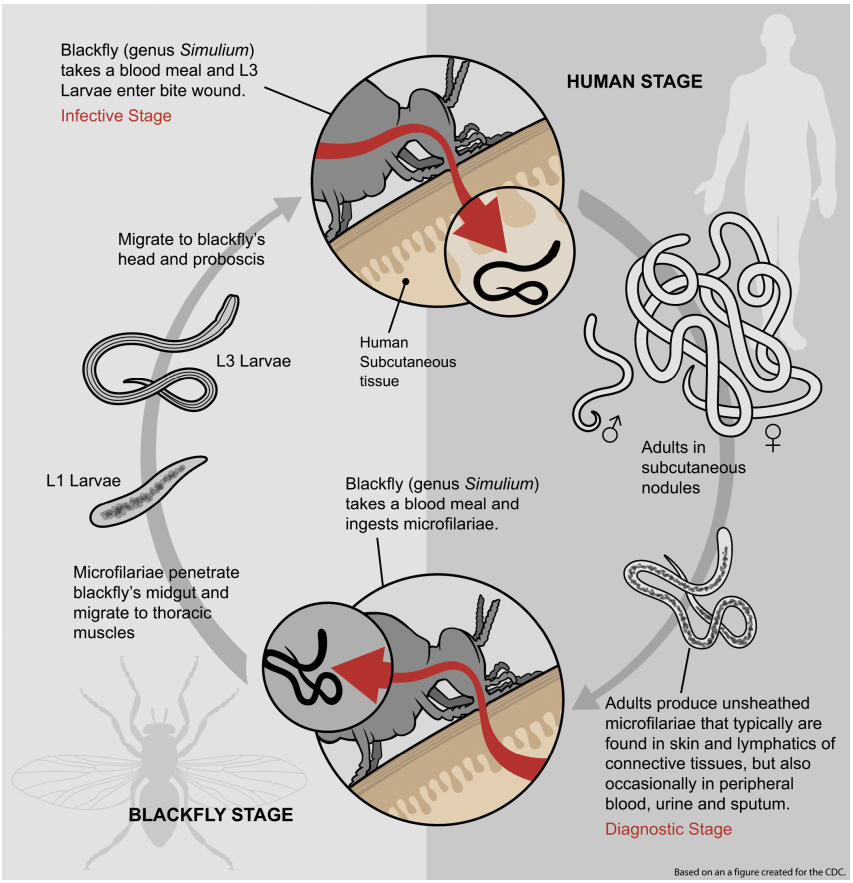
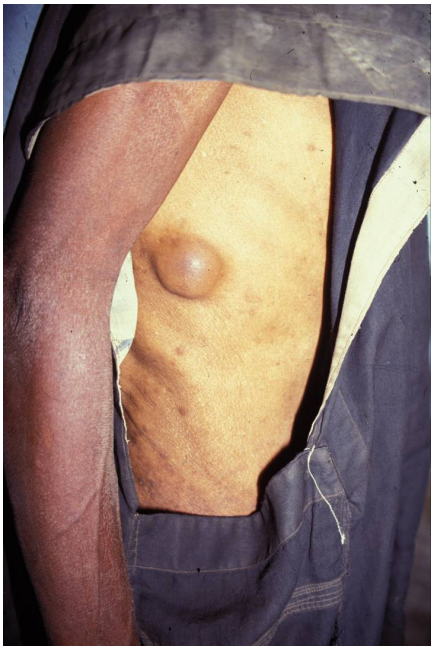


Figure 1.1: Life cycle of *Onchocerca volvulus*, distinguishing adult stages in humans and larval stages in humans and *Simulium* blackfly species. Reprinted from Basáñez et al. (2006).

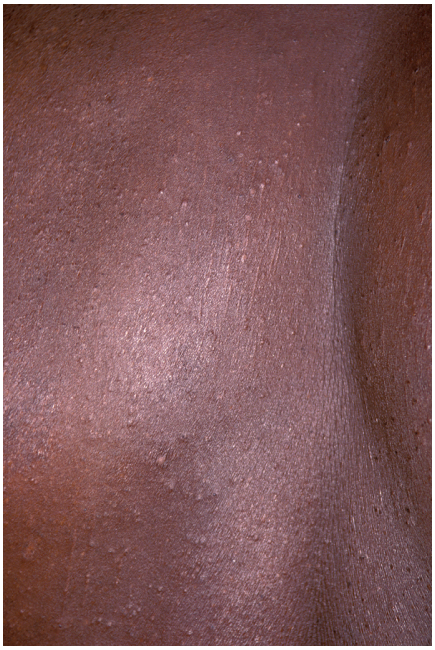
and damage to the retina and optic nerve, leading to visual impairment, and eventually, blindness (Bird, Anderson, and Fuglsang 1976; Anderson and Fuglsang 1977). Eye symptoms develop progressively over time and are most severe in individuals with high infection loads and long exposure to infection (Budden 1976; Thylefors and Tønjum 1980; Remme et al. 1989; Dadzie et al. 1990; Semba et al. 1990; Dadzie, De Sole, and Remme 1992). This thesis only considers the functional consequences of ocular lesions, visual impairment (visual

acuity $< 3/18$ and $\geq 3/60$ in the better eye) and blindness (visual acuity $< 3/60$ in the better eye), as defined by the WHO (1980). Visual impairment and blindness are more common in savanna areas than forest areas, which is thought to be due to the circulation of different parasite strains (Anderson et al. 1974b; McMahon et al. 1988; Dadzie et al. 1989; Remme et al. 1989). Fear of blindness and the geographical association with rivers have earned onchocerciasis its popular name *river blindness*.

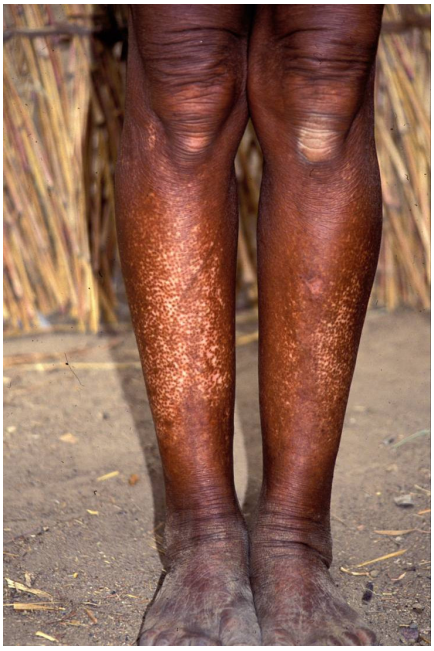
Onchocercal skin symptoms are broadly classified into a generalized form and a hyperreactive form. The more common, generalized form is characterized by presence of any of the following: subcutaneous nodules (Figure 1.2a), reactive skin disease (acute and chronic onchocedermatitis; Figure 1.2b), troublesome itch, skin depigmentation (typically located on the shins, called *leopard skin*; Figure 1.2c), premature skin atrophy (age < 50), and inguinal lymphadenopathy (*hanging groin*; Figure 1.2e) (Murdoch et al. 1993; Murdoch 2010). Often, multiple skin symptoms are present in the same individual, and symptoms may evolve into one another. Nodules, reactive skin disease, and troublesome itch are reversible conditions that usually affect all ages; their prevalences quickly increase with age, leveling off at about 20 years. In contrast, leopard skin, atrophy, and hanging groin are more or less irreversible conditions that mainly affect those who have experienced long and intense exposure to infection (i.e. the elderly) (WHO 1987; Murdoch et al. 2002). In a few individuals, infection with *O. volvulus* may lead to a chronic hyperreactive, severly itching onchodermatitis affecting a single or two symmetrical limbs (Figure 1.2d). This condition is called lichenified onchodermatitis; in Yemen, where it is believed to occur most often, it is also known as *sowda* (Arabic for 'black', referring to hyperpigmentation of the skin) (Anderson, Fuglsang, and al-Zubaidy 1973). This condition is associated with low mf densities in the skin, few nodules containing few adult worms, and a distinct host immune response, suggesting that these individuals are able to clear mf and ward off infective stage L3 larvae (Brattig 2004). It has not yet been described to what extent skin symptoms overlap with eye symptoms in individuals.



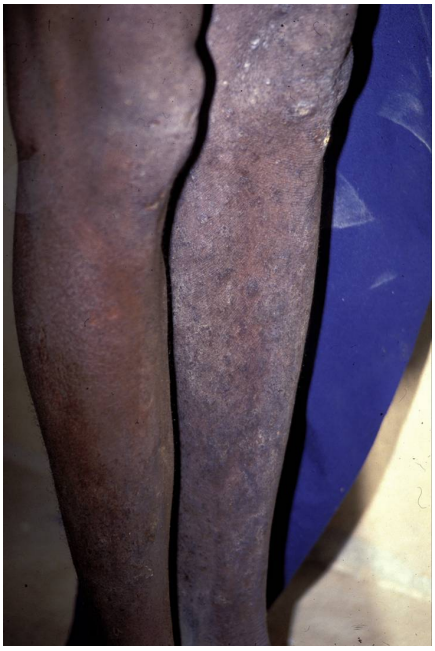
(a) Large nodule, or onchocercoma, overlying a rib. With permission from ME Murdoch (1992).



(b) Acute papular onchodermatitis on the back. With permission from ME Murdoch (1992).

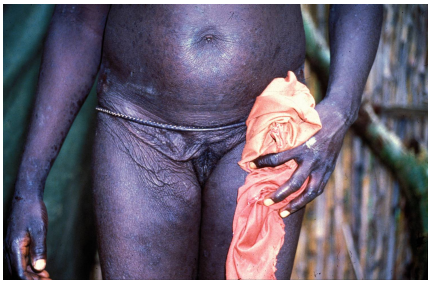


(c) Depigmentation on the shins. Reprinted with permission from ME Murdoch (2008).

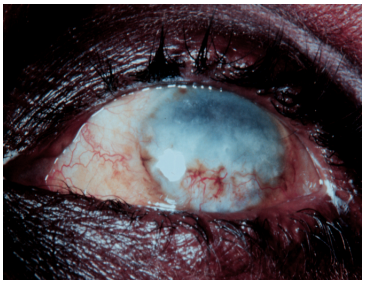


(d) Lichenified onchodermatitis affecting one leg in an 18 year old male. Reprinted with permission from ME Murdoch (2008).

Figure 1.2: Symptoms of onchocerciasis (continued on next page).



(e) Hanging groin in a female. Reprinted with permission from ME Murdoch (1992).



(f) Corneal scarring. Printed with permission from IE Murdoch.

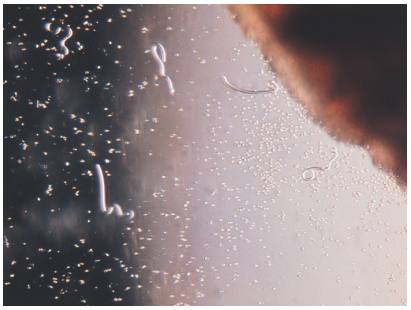
Figure 1.2: Symptoms of onchocerciasis (continued).

Apart from eye and skin symptoms, other, less common symptoms have been attributed to infection with *O. volvulus*, such as epilepsy (Pion et al. 2009; Pion and Boussinesq 2012), hyposexual dwarfism or Nakalanga syndrome (Kipp et al. 1996), and head-nodding syndrome (Winkler et al. 2008; Kaiser, Pion, and Boussinesq 2009; Centers for Disease Control and Prevention (CDC) 2012; Williams 2012). However, it is not clear how these symptoms are caused by infection with *O. volvulus*, or whether they occur in all endemic areas.

Diagnosis

There are several methods for diagnosing infection with *O. volvulus*, two of which are commonly used in population surveys in Africa. First, skin snipping is a classical method to diagnose infection in individuals via detection of mf in the skin. It relies on taking usually one or two small skin biopsies (*skin snips*) with a Walser or Holth corneoscleral punch (Figure 1.3a; Moreau, Prost, and Prod'hon 1978). In Africa, skin snips are usually taken from the skin over the iliac crests, whereas in the Latin Americas, they are usually taken from the shoulders, as these are the sites where skin mf are most abundant (related to the location of adult worms and the height at which *Simulium* flies preferably fly and bite). After incubation in a medium—usually saline or distilled water—for a variable amount

(a) Taking a skin snip with a Holth corneoscleral punch. Printed with permission of M Boussinesq.



(b) Microscopic examination of a skin snip, showing five emerged microfilariae. Reprinted with permission from Peters and Pasvol (2007).

Figure 1.3: Skin snipping.

of time (usually between 30 minutes and 24 hours), the specimens are microscopically examined for mf that may have emerged from the snip (Figure 1.3b). Sensitivity of skin snipping is highest when using saline and a long incubation time (Collins et al. 1980; Newell 1997), and is relatively low at low levels of infection (Taylor et al. 1989). Specificity is close to 100 %, unless emerging mf are confused with the (relatively rare) filarial species *Mansonella streptocerca* and *Dracunculus medinensis*. The results of skin snipping surveys are usually expressed as the proportion of the population with mf in the skin (*mf prevalence*) and/or the community microfilarial load (*CMFL*), which is the geometric mean number of mf per skin snip in people aged $\geq$ 20 years (Remme et al. 1986). Skin snipping results are a good indicator of the intensity of infection during and after control, as they reflect the potential for transmission in a population.

Second, for rapid evaluation of infection levels in a community, nodule palpation is often used as an alternative to skin snipping. The method relies on the detection of subcutaneous nodules harbouring adult worms. Nodule palpation is a non-invasive, cheap, though relatively crude method, requiring little equipment, and with the benefit that it is easily applicable on a wide scale (Ngoumou and Walsh 1993). The prevalence of nodules is higher in males and increases with age, up to the age of about 20 years (after which it

stabilizes). To maximize the sensitivity for detecting presence of infection in a community, nodule prevalence surveys usually target adult males aged $\geq$ 20 years (Ngoumou and Walsh 1993; Noma et al. 2002). Performed by experienced physicians, nodule palpation is a highly specific test for infection (Albiez, Büttner, and Duke 1988; Fischer et al. 1993). Sensitivity for detection of infection at individual level is relatively low, especially in case of low intensity infection. Therefore, nodule palpation is not suitable for diagnosing infection in individuals. Its value for assessing the impact of control interventions is currently under evaluation.

In some studies, nodules are excised and examined for presence and condition of adult worms (e.g. after drug treatment of the host). Examination of worms can be performed either histologically (Albiez et al. 1988) or by means of embryograms after collagenase digestion of the nodule (Schulz-Key 1988; Duke 1990), which are two comparable methods (Büttner et al. 1988). Presence of adult worms can be considered definite proof for infection, though there always is a risk of missing deep-tissue nodules, resulting in a false-negative diagnosis (Albiez 1983; Duerr et al. 2001).

After prolonged control interventions, skin snipping and nodule palpation may give the false impression of zero infection whereas infection may still be present at very low levels, and transmission may be ongoing. Therefore, more sensitive tests are being developed, such as the DEC (diethylcarbamazine) patch test, PCR (polymerase-chain-reaction) testing of skin material, and serological tests (Boatin et al. 2002; Rodríguez-Pérez, Unnasch, and Real-Najarro 2011). As an alternative to testing of humans, it is also possible to assess transmission of infection by testing *Simulium* flies. For example, fly dissection may reveal presence of larvae. However, this technique requires experienced entomologists and technicians, human bait, a lot of time, and may lead to false-positives due to presence of other *Onchocerca* species that are morphologically indistinguishable from *O. volvulus* (e.g. *O. ochengi*, which causes bovine onchocerciasis). Rather, fly catching combined with pool-screening of flies for presence of parasite DNA is a promising tool for assessing transmission (Katholi and Unnasch 2006; Gopal et al. 2012).

Treatment

In the past, onchocerciasis was treated intravenously with the macrofilaricidal drug suramin. However, after the last trials in the nineties that tried to identify the minimum treatment regime (Awadzi et al. 1995), it was finally abandoned because of severe, and sometimes fatal drug toxicity (Awadzi 2003). Likewise, diethylcarbamazine, an oral drug still used in the treatment of lymphatic filariasis, was abandoned in the nineties as it causes extremely intense itching and possible damage to the eye because of its instant microfilaricidal effect (Awadzi 2003). Excision of palpable nodules significantly reduce mf levels and transmission (Albiez 1985; Guderian et al. 1987; Guderian 1988), but is too cumbersome and expensive to perform on a large scale.

The drug ivermectin is currently the most widely applied treatment for onchocerciasis. A single oral treatment of $150\,\mu g\,kg^{-1}$ clears 95 % of the mf from the skin within a week, and 99 % within one to two months (*microfilaricidal* effect). Production of new mf by the adult female worms is temporarily halted, and only from three months onwards after treatment, the skin is gradually repopulated with mf (Basáñez et al. 2008). In addition to this, it is thought that ivermectin also irreversibly reduces the capacity of adult female worms to produce mf (Plaisier et al. 1995; Bottomley et al. 2008), and that it may kill a small proportion of adult worms (*macrofilaricidal* effect) (Gardon et al. 2002; Cupp and Cupp 2005; Duke 2005). Through these mechanisms, ivermectin prevents progression of morbidity in treated individuals, and slows down transmission of onchocerciasis in treated communities. The main safety concern regarding ivermectin is that it can cause encephalopathy in individuals who are heavily infected with *Loa loa* (eye worm), which is also endemic to parts of Africa (Gardon et al. 1997; Awadzi 2003; Boussinesq 2006). Other than that, ivermectin is a relatively safe drug, causing only mild, managable side-effects, with the probability of side-effects being highest in heavily infected individuals (Rothova et al. 1989), but declining after repeated treatments (i.e. when mf levels are lower) (Van der Lelij et al. 1990). Given this favourable safety profile, ivermectin was registered for mass treatment against onchocerciasis in 1987. Merck, the pharmaceutical company that

produces ivermectin, has pledged to donate ivermectin for mass treatment of onchocerciasis for as long as necessary (Walsh 1987; Colatrella 2008; Thylefors 2008), opening the way for large scale control programs.

Recently, doxycyclin, a classic antibiotic drug that depletes the parasite of its *Wolbachia* endosymbionts, has received a lot of attention because of its permanently sterilizing and macrofilaricidal effects (Hoerauf 2008). Furthermore, the development of mf to stage L3 larvae from doxycyclin-treated hosts seems to be retarded compared to mf from untreated hosts (Albers et al. 2012). Therefore, doxycyclin is a possible alternative to ivermectin for people that are heavily co-infected with *L. loa* (Wanji et al. 2009; Tamarozzi et al. 2012). A major drawback of doxycyclin is that it should be given daily over the course of several weeks, making that there is considerable risk of non-compliance to the treatment regime. Last, the antihelminthic drug flubendazole has been proposed as a candidate for further development into an macrofilaricidal drug (Mackenzie and Geary 2011).

Global burden of disease

The disease burden of onchocerciasis can be subdivided in the reduction in quality of life, reduction in life expectancy, and the socio-economic burden imposed on individuals and societies. Quality of life is reduced through physical discomfort and disability (e.g. visual impairment, blindness, troublesome itch and consequent insomnia), and social stigma (e.g. social isolation because of disfiguring skin disease; Alonso, Murdoch, and Jofre-Bonet 2009). Especially in forest areas of Africa, where onchocercal blindness is relatively rare, skin disease contributes most to the burden of disease (Murdoch et al. 2002; Murdoch 2010). With regard to life expectancy, several studies have shown that blindness is directly associated with excess mortality in rural Africa (Prost and Vaugelade 1981; Kirkwood et al. 1983; Prost 1986; Taylor et al. 1991; Pion et al. 2002). Possibly, life expectancy is also reduced directly by infection and especially high infection loads, in a way yet to be determined (Little et al. 2004a; Walker et al. 2012).

Apart from the disease burden, onchocerciasis also causes a con-

siderable socio-economic burden. For instance, in the West African savanna, 250,000 km^2 of fertile river valley were previously abandoned due to fear of blindness from onchocerciasis, leaving valuable agricultural resources unused (WHO 1987). Also, blindness considerably reduces the economic productivity of an individual in rural Africa, both through disability and excess mortality (Benton 1998). Similarly, infection and troublesome itch have been associated with lower income among coffee plantation workers, presumably because they are absent from work more often than individuals without infection or itch (Workneh, Fletcher, and Olwit 1993; Kim 1997). Another socio-economic aspect of the burden of onchocerciasis is that infection and the associated symptoms may impede optimal physical and/or cognitive development of children, reducing their potential to thrive. For instance, children of infected mothers have been reported to receive breast-feeding for a shorter period of time, because mothers suffer from severely itching skin lesions (Amazigo 1994). Also, troublesome itch in children may cause problems to concentrate in school. Even more directly, epilepsy and especially nodding syndrome are both conditions associated with mental retardation.

The burden of any disease is commonly expressed in terms of disability-adjusted life years (DALYs) lost. The DALY is a health metric that is the sum of the years of life lost due to excess mortality, and the years lived in disability, weighted by some disability weight representing the loss of quality of life (Mathers, Ezzati, and Lopez 2007). For instance, consider a person who turns blind at 50 years of age, lives another 10 years with disability from blindness, which reduces quality of life by 60 %. Hypothetically, without blindness, this person might have lived up to the age of 75 years of age (based on the life-expectancy of non-blind peers). In this case the burden of disease is expressed as 21 DALYs lost: 6 years of disability-adjusted life ($60\% * [60 - 50]$) plus 15 years of life ($75 - 60$).

Onchocerciasis causes a considerable global burden of disease, and 99 % of this burden can be found in Africa where most people at risk for infection live (approximately 100 million compared to 0.5 million in Latin America and even fewer in Yemen). Globally, 1.99 million DALYs were lost due to onchocerciasis in 1995

and 1.49 million DALYs in 2003 (Remme et al. 2006)). However, the disease burden of onchocerciasis needs to be quantified more accurately. By now, these estimates are outdated and need to be updated, taking account of the impact of ongoing control programs on the epidemiology and disease burden of onchocerciasis. Furthermore, the aforementioned and previous estimates of the global burden of onchocerciasis (Murray and Lopez 1996; Remme 2004) were based on national registry data, which are known to be incomplete, and do not consider the burden of disfiguring skin disease, leading to an underestimation of the disease burden.

Control programs

Onchocerciasis Control Programme

In 1975, the Onchocerciasis Control Programme (OCP) was set up with the aim to eliminate onchocerciasis as a public health problem from West Africa, where fear of blindness had led to abandonment of fertile river valleys, delaying socio-economic development (Boatin 2008). Originally, the program started in seven countries, but was expanded during subsequent years, eventually including 11 countries (Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Senegal, Togo), covering a population at risk for onchocerciasis of over 78 million people by its end in 2002. Infection levels were mapped by means of skin snipping surveys. The program's main intervention strategy was to interrupt transmission by suppressing the blackfly population (vector control) until the existing worm population in humans was too old and few in numbers to sustain itself. Suppression of the blackfly population was achieved by weekly spraying of river basins where blackflies were known to breed (larvidicing). It was estimated that 14 years of continuous larviciding would be sufficient to completely interrupt transmission of infection (Plaisier et al. 1991a). This duration was reduced to 12 years when the drug ivermectin became available in 1987, and mass treatment with ivermectin was implemented in addition to larviciding. In forest areas of southern Sierra Leone, vector control was not possible due to dense vegetation, and onchocerciasis was controled solely by means of ivermectin mass treatment. In the

OCP program, ivermectin mass treatments were implemented via a top-down approach, by means of mobile teams that distributed the drugs.

As of 2002, onchocerciasis is no longer considered a public health problem in West Africa. For a number of foci within former OCP program areas, focal elimination of onchocerciasis (i.e. interruption of transmission) has even been reported (Diawara et al. 2009). However, in other areas it has been difficult to control onchocerciasis due to migration of humans (civil unrest) and flies (carried by the wind, flies may travel up to 400 km). After the closure of OCP in 2002, these areas were designated as *Special Intervention Zones* (SIZ), and coordination of control programs in SIZ was transferred to the African Programme for Onchocerciasis Control (see below) (Yaméogo 2008). In addition, many West African countries themselves still coordinate and execute annual mass treatment in non-SIZ areas, without a clearly defined endpoint.

African Programme for Onchocerciasis Control

In 1995, the African Programme for Onchocerciasis Control (APOC) was established with the aim to eliminate onchocerciasis as a public health problem in areas not covered by the former OCP program, and in SIZ areas in West Africa. The main control strategy of APOC is ivermectin mass treatment, as larviciding is relatively expensive and moreover, ineffective in the forest areas of central Africa. In contrast to OCP, in APOC areas ivermectin mass treatment is entirely community directed, meaning that communities are themselves responsible for choosing a time and manner of ivermectin mass treatment (Sékétéli et al. 2002; Amazigo 2008). APOC in turn provides training for individuals (volunteers) responsible for distribution in a community. This strategy, coined community-directed treatment with ivermectin (CDTI), has proven to be an effective and cost-saving approach, and is able to sustain better coverage during political instability than top-down approaches.

To define areas eligible for ivermectin mass treatment, APOC has mapped, or has started mapping infection in potentially endemic countries not covered by OCP (Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo,

Equatorial Guinea, Ethiopia, Gabon, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, North Sudan, South Sudan, Uganda, and the United Republic of Tanzania). Mapping is performed by means of Rapid Epidemiological Mapping of Onchocerciasis (REMO), a method that relies on nodule palpation in a sample of 30 to 50 adult males from selected villages (Ngoumou and Walsh 1993; Noma et al. 2002). Figure 1.4 illustrates the distribution of infection in Africa, based on a spatial analysis (Kriging) of the REMO data. Based on the REMO surveys, which include over 14,000 villages so far, project areas (geographical implementation units for CDTI) have been defined in 16 countries (all aforementioned countries but Gabon, Kenya, Rwanda, and Mozambique), based on the minimum threshold value of 20 % nodule prevalence in adult males, which is deemed indicative of onchocerciasis being a severe public health problem. REMO surveys are still ongoing, especially in countries where earlier mapping was not possible due to political instability and civil unrest.

Information on the health impact of APOC is important for program evaluation and further policy making. Furthermore, it is pivotal for advocacy, as APOC depends entirely on donations from countries in the northern hemisphere, donation of drugs by the pharmaceutical industry, and the commitment of beneficiary governments and communities. To monitor program performance, APOC keeps record of the number of ivermectin treatments given and number of people living in each project area, as annually reported by community volunteers responsible for the distribution of ivermectin. These data provide insight into how CDTI has been scaled up over the years, both in terms of geographical coverage (number of villages treated) and therapeutic coverage (number of individuals treated). Furthermore, these data provide an estimate of the population at risk in CDTI target areas. To monitor the impact of CDTI on morbidity, APOC has performed morbidity impact surveys, both before and during control (Ozoh et al. 2011). However, because these surveys only cover a small number of sentinel sites that are probably not representative of the larger APOC regions in terms of infection, morbidity, and history of CDTI, they can not be used as a single source of information for estimating the health impact

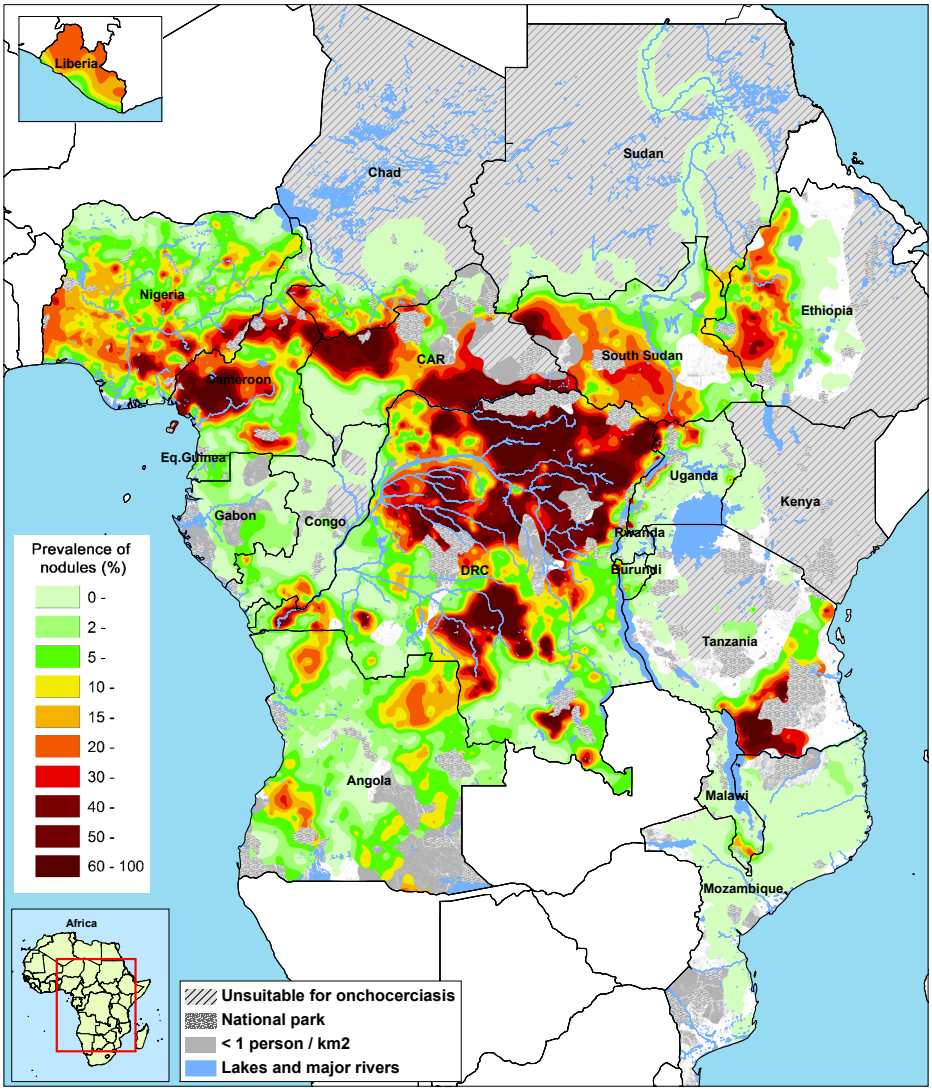


Figure 1.4: Geographical distribution of *Onchocerca volvulus* infection in terms of nodule prevalence in adult males prior to control, based on a spatial analysis (Kriging analysis) of REMO data from 14,115 villages available by 2013. The prevalence of nodules is an indicator of the level of onchocerciasis endemicity; above 20 % nodule prevalence, onchocerciasis is considered a severe public health problem. Printed with permission of the African Program for Onchocerciasis Control.

of APOC. Furthermore, these surveys do not consider the impact of ivermectin mass treatment on off-target diseases, such as soil-transmitted helminthiasis and ectoparasitic infections (Tielsch and Beeche 2004). Therefore, there is a need for a more comprehensive health impact assessment of APOC activities.

Currently, APOC is going through a paradigm shift from morbidity control to elimination of infection, where possible (APOC 2010). Eventually, ivermectin mass treatment may interrupt transmission and eliminate infection with *O. volvulus* from endemic areas, allowing CDTI to be suspended, although this will likely require many repeated annual treatment rounds (≥ 25 for highly endemic areas) (Winnen et al. 2002). Therefore, after the example of control programs in the Latin Americas, it has been proposed to increase the frequency of mass treatment in Africa to 'mop up' and eliminate onchocerciasis (Burnham 2007). However, the benefits of such a change in mass treatment frequency would depend on the current progress towards elimination, and would force significant changes on the control program in terms of expenses, logistics, and ivermectin production.

Latin America and Yemen

For the sake of completeness and comparison, a short summary of the situation regarding the control of onchocerciasis outside Africa is given here. In Latin America, the Onchocerciasis Elimination Program for the Americas (OEPA) has identified 13 foci of onchocerciasis transmission in six countries (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela), inhabited by approximately 500,000 people at risk of infection (Sauerbrey 2008). By means of initially 6-monthly, and now even 3-monthly mass treatment with ivermectin, implemented via mobile teams, OEPA has managed to interrupt transmission of onchocerciasis and stop ivermectin mass treatment in seven foci by 2010, and has most likely suppressed transmission in another two foci where mass treatment was ongoing by that time (Cupp, Sauerbrey, and Richards 2011). Onchocercal eye disease is reported to no longer occur. According to The Carter Center (www.cartercenter.org), by 2012, transmission of onchocerciasis has been entirely interrupted or suppressed in the Latin Americas,

with the exception of the border region of Venezuela and Brazil, deep in the Amazon rainforest where Yanomami indians live.

Up to 2012, political instability and civil unrest have prevented Yemen to develop a sustained large scale control program against onchocerciasis. Probably, several mass treatment programs have taken place, though little is publicly known about their location, duration, and degree of population coverage.

Mathematical modeling to guide control activities

Historically, mathematical modeling has played an important role in onchocerciasis control (Basáñez and Ricárdez-Esquinca 2001). In absence of animal models, it has helped to understand the biology of onchocerciasis and mechanisms behind the impact of control interventions. Furthermore, it has helped to evaluate control programs and inform policy makers what to expect from control interventions. Especially in resource-limited settings where routine large-scale collection of data for monitoring is not feasible (as is the case for Africa), mathematical models can provide useful information. As explained earlier, there is limited data on trends in onchocercal morbidity in Africa. However, there is good information on pre-control levels of infection and the history of control interventions. Through mathematical modeling based on these data, it is possible to estimate the health impact of onchocerciasis control in Africa.

Of the various mathematical models for onchocerciasis (Plaisier et al. 1990; Davies 1993; Habbema, van Oortmarssen, and Plaisier 1996; Basáñez and Ricárdez-Esquinca 2001; Filipe et al. 2005; Poolman and Galvani 2006; Duerr, Raddatz, and Eichner 2011), only two have been routinely used for program evaluation. First, there is the SIMONa (an updated version of SIMON (Davies 1993)), which has been routinely used by OEPA to evaluate the prospects of elimination of onchocerciasis from the Latin Americas. Second, there is ONCHOSIM (Plaisier et al. 1990; Habbema, van Oortmarssen, and Plaisier 1996), which has been routinely used for policy making and evaluation of OCP in West Africa. ONCHOSIM has been used to estimate the reproductive lifespan of *O. volvulus* worms

(Plaisier et al. 1991b), estimate ivermectin efficacy against *O. volvulus* worms and mf (Alley et al. 1994; Plaisier et al. 1995), guide OCP control activities in West Africa (Plaisier et al. 1991a, 1997), and predict the prospects of elimination of onchocerciasis from Africa (Winnen et al. 2002). Apart from the different geographical areas that these two models represent, another important difference between ONCHOSIM and SIMONa (and all other models) is that ONCHOSIM is the only model that simulates both infection and morbidity, and takes account of individual variation in exposure to infection and health care seeking behaviour. Therefore, for this thesis we exclusively used ONCHOSIM to estimate the health impact of onchocerciasis control in Africa.

ONCHOSIM is a microsimulation model, which means that it simulates the life histories of individuals and worms within individuals. The simulations are based on mechanisms that are reflective of human demography (as in a typical African rural village) and the biology of onchocerciasis and its black fly vector. In a simulation, individuals are born and die. During their life, individuals may contract multiple infections and transmit infection to others through exposure to fly bites, develop symptoms as a result of infection, and participate in control interventions (if applicable). Infection levels in the population are limited (i.e. infection levels do not increase infinitely) because of negative density-dependence in the uptake of skin mf by *Simulium* flies. In other words, with increasing infection levels, *Simulium* flies take up fewer and fewer additional skin mf. The effects of larviciding and ivermectin mass treatment are simulated by mechanisms that directly influence the simulated black flies and/or worms and mf. The user can specify moments in time at which the model generates output in terms of levels of infection (based on skin snipping as in the field) and morbidity. ONCHOSIM is a stochastic model, meaning that the simulated processes are governed by chance and that repeated simulations always result in slightly different predictions. By performing many repeated simulations, we can get an idea of the possible range of outcomes for a scenario. More details about the model will be given in Chapter 4 and Chapter 7.

To be able to link ONCHOSIM predictions to the REMO data,

it is necessary to translate the REMO data (nodule prevalence in adult males) to a measure of infection that is comparable to ONCHOSIM predictions regarding infection levels (prevalence of skin mf or CMFL). There is a simple conversion model to translate nodule prevalence in adult males to prevalence of skin mf in the general population (Remme 2004). This model is sufficiently accurate to translate REMO data to average mf prevalences for large geographical regions (e.g. project areas). However, it does not provide estimates of uncertainty for this translation. Modern statistical methods can provide a solution there, taking account of measurement error in the data and possible geographical variation in the association between nodule prevalence and mf prevalence or CMFL. Carrying through uncertainty when translating REMO data will be particularly important in future applications, such as evaluating the prospects of elimination of onchocerciasis (which are highly dependent on pre-control infection levels; Winnen et al. 2002).

Aims and outline of this thesis

The aim of this thesis is to quantify the health impact of onchocerciasis control in Africa, focussing mainly on the ongoing African Programme for Onchocerciasis Control. However, some of the findings and conclusions in this thesis will also be relevant for ongoing control efforts in West Africa and Latin America. To estimate the health impact of onchocerciasis control in Africa, the following research questions need to be answered:

1. What was the pre-control disease burden of onchocerciasis in Africa?

2. What has been the impact of ivermectin mass treatment, and what can be expected in the future?

In **Chapter 2**, we present a statistical analysis to relate nodule prevalence in adult males to skin mf prevalence in the general population, which allows ONCHOSIM predictions to be related to REMO data. In **Chapter 3**, we analyze patterns in concurrence of eye and skin symptoms due to onchocerciasis in individuals, with the objective to obtain information about the distribution of morbidity in

the African population, and to inform modelling and disease burden estimation. **Chapter 4** covers the estimated health impact of onchocerciasis control in APOC areas. **Chapter 5** provides a short update of the estimated health impact, based on updated disability weights. Next, **Chapter 6** covers the impact of APOC activities on diseases other than onchocerciasis that are also affected by ivermectin mass treatment. In light of APOC's paradigm shift from control to elimination, **Chapter 7** presents the expected impact of increasing mass treatment frequency on the prospects of elimination of onchocerciasis, and the associated program duration and number of mass treatment rounds. Finally, in **Chapter 8**, we discuss the answers to the research questions, some methodological aspects of using ONCHOSIM, and the future of onchocerciasis control in Africa and the possible role of modeling therein.

Chapter 2

Onchocerciasis: the pre-control association between prevalence of palpable nodules and skin microfilariae

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Abstract

The prospect of eliminating onchocerciasis from Africa by mass treatment with ivermectin has been rejuvenated following recent successes in foci in Mali, Nigeria and Senegal. Elimination prospects depend strongly on local transmission conditions and therefore on pre-control infection levels. Pre-control infection levels in Africa have been mapped largely by means of nodule palpation of adult males, a relatively crude method for detecting infection. We investigated how informative pre-control nodule prevalence data are for estimating the pre-control prevalence of microfilariae (mf) in the skin and discuss implications for assessing elimination prospects. We analyzed published data on pre-control nodule prevalence in males aged $\geq$ 20 years and mf prevalence in the population aged $\geq$ 5 years from 148 African villages. A meta-analysis was performed by means of Bayesian hierarchical multivariate logistic regression, accounting for measurement error in mf and nodule prevalence, bioclimatic zones, and other geographical variation. There was a strong positive correlation between nodule prevalence in adult males and mf prevalence in the general population. In the forest-savanna mosaic area, the pattern in nodule and mf prevalence differed significantly from that in the savanna or forest areas. We provide a tool to convert pre-control nodule prevalence in adult males to mf prevalence in the general population, allowing historical data to be interpreted in terms of elimination prospects and disease burden of onchocerciasis. Furthermore, we identified significant geographical variation in mf prevalence and nodule prevalence patterns warranting further investigation of geographical differences in transmission patterns of onchocerciasis.

Introduction

In 1995, the World Health Organization launched the African Programme for Onchocerciasis Control (APOC). At that time, APOC aimed to control morbidity due to onchocerciasis (river blindness) in Africa, with a focus on those countries not covered by the previous Onchocerciasis Control Programme in West Africa (OCP). Since 1995, APOC has successfully coordinated mass treatment with ivermectin in sixteen onchocerciasis-endemic African countries (Coffeng et al. 2013b). Until recently, elimination of onchocerciasis from African foci was deemed to be not achievable by means of mass ivermectin treatment alone, considering the large size of the transmission zones, the mobility of the insect vectors and human populations, and poor compliance with mass treatment in some areas (Dadzie, Neira, and Hopkins 2003). However, following the first reports of elimination of onchocerciasis from foci in Mali, Senegal, and Nigeria by mass treatment alone (Diawara et al. 2009; Tekle et al. 2012; Traore et al. 2012), there is renewed interest in elimination of onchocerciasis from Africa (Mackenzie et al. 2012).

Pre-control infection levels are an important predictor of morbidity levels (Dadzie et al. 1989; Remme et al. 1989; Dadzie et al. 1990) and the duration of onchocerciasis control programs required to achieve elimination of infection (Plaisier et al. 1997; Winnen et al. 2002). High pre-control levels of infection indicate circumstances that are favorable for intense transmission in terms of vector abundance, proximity to vector breeding sites, high vectorial capacity and competence, etc. In such circumstances, mass treatment with a drug such as ivermectin, which is predominantly microfilaricidal, but has a lesser impact on adult worm survival, needs to be continued for a long time and at high therapeutic and geographical coverage before it can be stopped without considerable risk of recrudescence of infection. Progress towards elimination of onchocerciasis from APOC areas is currently being evaluated by means of ongoing skin snipping surveys that measure levels of infection in terms of presence and density of microfilariae (mf) in the skin of the general population (Tekle et al. 2012). In contrast, precontrol levels of infection in APOC areas have been quantified by the REMO method (rapid epidemiological mapping of onchocerciasis), which is based on

the palpation of subcutaneous nodules containing adult Onchocerca volvulus worms in a sample of 30 to 50 males aged $\geq$ 20 years in villages selected using a standardized selection procedure (Ngoumou and Walsh 1993; Noma et al. 2002). Results from pre-control and ongoing surveys will have to be compared, even though the REMO method is much cruder for detecting presence and intensity of infection than skin snipping. Therefore, it is important to assess how informative pre-control nodule palpation data are, and when and whether they can be reliably translated to equivalent measures of skin microfilariae. In other words, there is need for a quantitative model describing the association between pre-control nodule prevalence and pre-control presence of skin microfilariae, which takes into account the differences between the two methods as well as other covariates. Such a model would also allow estimates of pre-control nodule prevalence to be related to the large body of literature on the correlation between mf prevalence and prevalence of onchocercal morbidity, allowing better estimation of the disease burden of onchocerciasis.

We present a statistical model describing the association between pre-control nodule prevalence in adult males and precontrol mf prevalence in the general population. Quantitative relationships for this association have been previously described, but were based on smaller number of surveys, did not provide estimates of uncertainty around parameter estimates and model predictions, and did not account for geographical variation or the relatively small sample sizes routinely used for the nodule palpation method, resulting in attenuation bias (due to measurement error in nodule prevalence; Whitworth and Gemade 1999; Vivas-Martínez et al. 2000; Kipp and Bamhuhiiga 2002; Remme 2004). In this study, we analyzed original pre-control data, accounting for these factors, and using Bayesian statistical methods, well known for providing robust uncertainty estimates around model parameters.

Table 2.1: Characteristics of data used for modeling the association between prevalence of nodules and microfilariae.

Area	Number of villages	Number of males examined for nodules	Number of individuals from general population examined for microfilariae in the skin	Bioclime	Vector responsible for transmission (*Simulium* spp)
Kigoyera Parish, Uganda[a]	8	667	2,085	Forest	*S. neavei* s.s.[a]
Onchocerciasis Control Programme[bc]	26	1,386	5,273	Savanna	*S. damnosum* s.s. and *S. sirbanum*[b]
Kaduna, Nigeria[c]	33	1,822	7,274	Savanna	*S. damnosum* s.s. and *S. sirbanum*[d]
Lekié, Cameroon[e]	19	806	3,430	Degraded forest	*S. squamosum* B[f]
Mbam, Cameroon[e]	34	1,354	6,190	Forest-savanna mosaic	*S. squamosum* B[f]
Vina, Cameroon[c]	19	1,122	4,266	Savanna	*S. damnosum* s.s. and *S. sirbanum*[g]
Faro, Cameroon[e]	9	368	1,257	Savanna	*S. damnosum* s.s. and *S. sirbanum*[h]

[a] Fischer et al. (1993) [b] Remme et al. (1989) [c] WHO (1992); Remme (2004) [d] Vajime and Gregory (1990) [e] Unpublished [f] Traoré-Lamizana et al. (2001) [g] Traoré-Lamizana and Lemasson (1987) [h] Quillévéré, Hougard, and Prud'hom (1990)

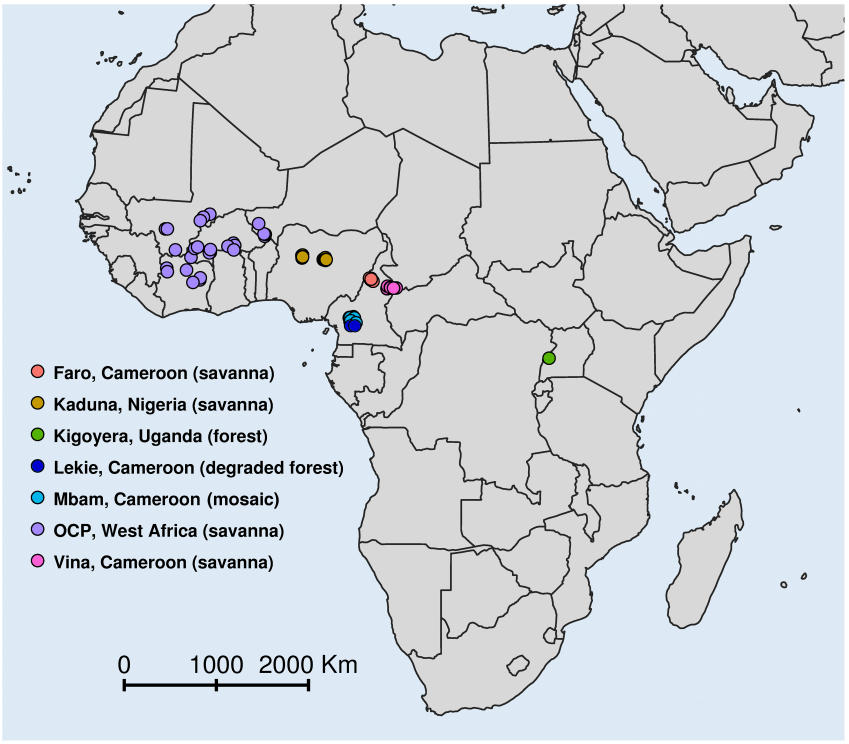

Figure 2.1: Locations of study sites.

Materials and methods

Data and Study Sites

We analyzed original data on pre-control nodule prevalence in adult males ($N = 7,525$ individuals) and mf prevalence in the population aged five years and above ($N = 29,775$ individuals) from 148 villages in seven geographical areas including countries in the former OCP area, and foci in Cameroon, Nigeria, and Uganda, which are part of APOC (Table 2.1, Figure 2.1). Most of these data have been previously published (Remme et al. 1989; WHO 1992; Fischer et al. 1993; Remme 2004), except for part of the data from Cameroon. The simuliid vectors responsible for transmission in each area have been described previously (Table 2.1; Traoré-Lamizana and Lemasson 1987; Remme et al. 1989; Quillévéré, Hougard, and

Table 2.2: Weights used to standardize prevalence of microfilariae in the skin. Standardization weights were based on the reference population of the Onchocerciasis Control Programme.

Age	Male	Female
5–9	0.091	0.078
10–14	0.090	0.077
15–29	0.129	0.138
30–49	0.123	0.146
≥ 50	0.063	0.064

Prud'hom 1990; Vajime and Gregory 1990; Fischer et al. 1993; Traoré-Lamizana et al. 2001). In all areas, data on nodule and mf prevalence had been collected simultaneously (except for Nigeria, where nodule palpation took place six to twelve months after skin snipping, though still before the start of control interventions). All data on mf prevalence were based on taking two skin snips (one from each iliac crest) from each individual examined, which were incubated in saline for 24 hours, and village-level prevalence values were age- and sex-standardized according to the reference OCP population (direct standardization, Table 2.2). Then, we calculated the standardized number of mf positive persons in a village by multiplying the standardized prevalence with the sample size, and rounding to the nearest integer. Nodule prevalence was based on palpation-based detection of nodules that could be attributed to onchocerciasis with reasonable certainty, similar to the methodology used for mapping of infection in APOC areas; i.e. nodules of uncertain etiology (e.g. possible enlarged lymph nodes) were excluded (Ngoumou and Walsh 1993). All data were used with permission of the authors who originally collected such data, and were analyzed anonymously.

Statistical Methods and Model Fitting

The association between village-level mf prevalence and nodule prevalence was quantified in a meta-analysis by means of hierarchical multivariate logistic regression, i.e. logistic regression where the predicted outcome is a set of correlated binary random variables rather

than a single binary random variable. A hierarchical approach was taken to account for unmeasured sources of variation between geographical areas. A multivariate approach was taken to account for measurement error in each measure of infection. This approach prevents regression of model coefficients towards zero (attenuation bias) as we do not have to assume that there is no measurement error in the explanatory variable (e.g. either nodule or mf prevalence), an assumption inherent to univariate regression (Carroll et al. 2006).

We extended the ordinary hierarchical logistic regression model to a multivariate model simultaneously predicting m binary outcomes:

$$\text{logit}(\pi_{ij,m}(y_{ij,m}|X_{ij}, \beta_m, n_{ij,m})) = X_{ij}^T \beta_m + \epsilon_{ij} + \epsilon_j \qquad (2.1)$$

where $\pi_{ij,m}$ is the probability of finding y cases of the m-th binary outcome ($m = 1$: presence of microfilariae in the skin; $m = 2$: presence of nodules in adult males) among n_m observed individuals from the i-th unit (village) and the j-th cluster (geographical area). The error terms ϵ_{ij} and ϵ_j (each consisting of m components) represent the variation (random effects) in infection levels within and between the j geographical areas, respectively. For each village there is a set of observed covariates X_{ij}, and for each of the m predicted binary outcomes there is a set of parameters bm (fixed effects), where the intercepts $\beta_{0,m=1}$ and $\beta_{0,m=2}$ represent the mean log odds of presence of mf in the general population (all those aged ≥ 5 years) and nodules in adult males. To explain possible large differences between geographical areas related to bioclime, parasite strains and clinical manifestations in onchocerciasis (Zimmerman et al. 1992), we included a set of coefficients for bioclimatic zone in the model. Here, the parameters $\beta_{1,m=1}$ and $\beta_{1,m=2}$ represent the log odds ratio of observing microfilariae in the skin and subcutaneous nodules in forest areas (including degraded forest and forest-savanna mosaic areas), relative to savanna areas. Correlation between nodule and mf prevalence was modeled by assuming a multivariate normal distribution for the m components of the error term at each level of analysis. See Appendix A, section "Model description" for a more detailed description of the model.

To account for measurement error due to misclassification of nodules (e.g. classifying lymph nodes as onchocercal nodules due to

Table 2.3: Model parameter estimates from Bayesian hierarchical multivariate logistic regression of infection prevalence data. The model predicts the joint distribution of prevalence of nodules in adult males (age ≥ 20) and presence of microfilariae (mf) in the skin of the general population (age ≥ 5).

Parameter[a]	Interpretation	Median[b]	Lower bound[b]	Upper bound[b]
$\text{logit}^{-1}(\beta_{0,m=1})$	Average fraction of general population with mf in the skin (excluding Mbam)	0.68	0.55	0.78
$\text{logit}^{-1}(\beta_{0,m=2})$	Average fraction of adult males with onchocercal nodules (excluding Mbam)	0.51	0.36	0.67
$\exp(\beta_{1,m=1})$	Odds ratio of presence of mf in the skin in Mbam compared to other areas	4.17	1.04	16.69
$\exp(\beta_{1,m=2})$	Odds ratio of presence of nodules in Mbam compared to other areas	2.69	0.45	14.57
$\sigma_{ij,m=1}$	Standard deviation of log odds of presence of mf within geographical areas	0.98	0.87	1.11
$\sigma_{ij,m=1}$	Standard deviation of log odds of presence of nodules within geographical areas	0.89	0.77	1.03
ρ_{ij}	Correlation of log odds of presence of nodules and mf within geographical areas	0.84	0.77	0.90
$\sigma_{j,m=1}$	Standard deviation of average log odds of presence of mf between geographical areas	0.55	0.22	1.24
$\sigma_{j,m=2}$	Standard deviation of average log odds of presence of nodules between geographical areas	0.69	0.31	1.50
ρ_j	Correlation of average log odds of presence of nodules and mf between geographical areas	0.88	0.28	1.00
Specificity	One minus the probability of misclassifying a subcutaneous nodule as onchocercal	0.99	0.98	1.00

[a] For ease of interpretation, parameter estimates have been transformed to an intuitive scale, where possible (inverse logit transformation for intercepts and exponents for other fixed effects parameters). See Appendix A for a detailed description of the model and its parameters.

[b] Median and lower and upper bounds were defined as the 50^{th}, 2.5^{th}, and 97.5^{th} percentiles of the simulated posterior distributions, respectively.

imperfect specificity; or failing to detect at least one subcutaneous onchocercal nodule when one or more are present, due to imperfect sensitivity), we added parameters to the model for specificity and sensitivity of nodule palpation, allowing these to be estimated from the data. Prior information for parameter values was based on the literature. A wide range of values is reported for specificity (60 %–99 %), based on various definitions (Albiez, Büttner, and Duke 1988; Fischer et al. 1993; Vivas-Martínez et al. 2000; Duerr, Raddatz, and Eichner 2008). We assumed that when performed by physicians experienced in recognizing onchocercal nodules, specificity of nodule palpation is between 98 % and 100 %, based on the report of finding only four non-onchocercal nodules among 312 extirpated nodules (Fischer et al. 1993). Further, we assumed that sensitivity increases with level of infection, reflecting the notion that detection of at least one nodule is more likely in a person with many onchocercal nodules than in a person with few or only one (Duerr, Raddatz, and Eichner 2008). In literature, no values for sensitivity of nodule palpation as a method for detecting onchocercal nodules are reported. In the current study, sensitivity was assumed to increase linearly from some unknown minimum sensitivity (value between 60 % and 100 %) for nodule prevalences close to zero (when persons with nodules have few nodules) to 100 % for nodule prevalence of 100 %. The choice of a linearly increasing pattern was based on a simulation exercise in which we examined the association between the proportion of the nodule carriers that is detected and the 'true' nodule prevalence, given simulated true nodule counts (assuming a negative binomial distribution of counts within a village) and some probability to detect each nodule (minimum sensitivity). A sensitivity analysis showed that the model fit and model predictions did not change when assuming different values for minimum sensitivity of nodule palpation at low infection levels (60 %, 80 %, or 100 %). This is explained by the fact that sensitivity is most important for high prevalence settings (for which we assume sensitivity is high anyway), and far less important in low prevalence settings (where misclassification is largely governed by specificity). Therefore, we simplified the final model by leaving out the parameter for sensitivity, effectively assuming 100 % sensitivity of nodule palpation for all infection levels.

Based on the model described above, we estimated the conditional distribution of mf prevalence in a hypothetical village outside the dataset, given an estimate of the 'true' nodule prevalence in adult males (i.e. corrected for misclassification of nodules). We assumed that nodule prevalence estimates were based on a sample of 30 adult males, the minimal sample size used in REMO surveys (Ngoumou and Walsh 1993; Noma et al. 2002). See Appendix A, section "Model application" for a more detailed description of the methods for predicting mf prevalences in hypothetical villages.

The model was fitted to the data in a Bayesian framework. Posterior distributions of parameters and predictions were simulated in JAGS[1], a program for analysis of Bayesian models using Markov Chain Monte Carlo (MCMC) simulation based on the Gibbs sampling algorithm (see Appendix A, section "Model specification in JAGS" for code). Simulations in JAGS were set up and analyzed in R (version 2.14.2; R Core Team 2013), using packages *rjags*[2] and *R2jags*[3]. Improvements in model fit by addition of parameters were assessed via the deviance information criterion (DIC), a generalization of Akaike's information criterion for hierarchical models (lower values indicate better fit, taking into account model deviance and the effective number of parameters in the model) (Spiegelhalter et al. 2002). See Appendix A, section "Parameter estimation" for further details about model fitting and checking of model convergence.

The final fit of the model to the data was evaluated by means of mixed posterior predictive checks (Marshall and Spiegelhalter 2003; Green, Medley, and Browne 2009). In this procedure, the number of individuals positive for mf and nodules in each village was resampled 40,000 times from the estimated joint posterior distribution of model parameters, including resampling of all random effects, and the resulting replicate dataset was compared to the original data.

[1] JAGS version 3.2.0; Martyn Plummer, 2012, http://mcmc-jags.sourceforge.net.

[2] *rjags* version 3–5, Martyn Plummer, 2011, http://CRAN.R-project.org/package=rjags.

[3] *R2jags* version 0.03-06, Yu-Sung Su, 2011, http://CRAN.R-project.org/package=R2jags.

Results

The median nodule prevalence in males aged $\geq$ 20 years was 58 % (range: 2 %–100 %), and the median mf prevalence in the population aged five years and above was 74 % (4 %–99 %). The median sample size for nodule prevalence in a village was 42 (range: 9–181). The median sample size for mf prevalence in a village was 167 (33–727). Nodule prevalence in adult males was strongly positively correlated with mf prevalence in the general population (Table 2.3). There was significant geographical variation in patterns of nodule and mf prevalence; in a model without any coefficients for bioclime, the DIC increased from 1,918 to 1,920 when error term ϵ_j was omitted. Point estimates of ϵ_j were very similar for savanna and forest areas, with the exception of Mbam, Cameroon (forest-savanna mosaic), for which mf prevalence was relatively high compared to other areas. In line with this, the model fit did not improve when a fixed effect parameter for bioclime was added to the model. However, the model fit improved significantly when modeling the difference between Mbam and all other areas as a fixed effect (DIC 1,913 vs. DIC 1,918), indicating that mf prevalences in Mbam were significantly higher than those in other areas (Table 2.3, Figure 2.2). After this adaptation of the model, there was still significant variation in patterns of nodule and mf prevalence between geographical areas due to other, unmeasured variables (the DIC increased to 1,921 when error term ϵ_j was omitted). Further, there was considerable uncertainty in the predictions for mf prevalence, based on nodule prevalence in a sample of 30 males from a hypothetical village outside the dataset (Figure 2.3). Mixed posterior predictive checks showed that the model fitted well to the data (Figure 2.4). Only three villages – all from different regions, and all with relatively low infection levels compared to other villages from the same region – deviated significantly from the model predictions.

Discussion

We investigated the association between pre-control nodule prevalence in adult males (aged $\geq$ 20 years) and pre-control mf prevalence

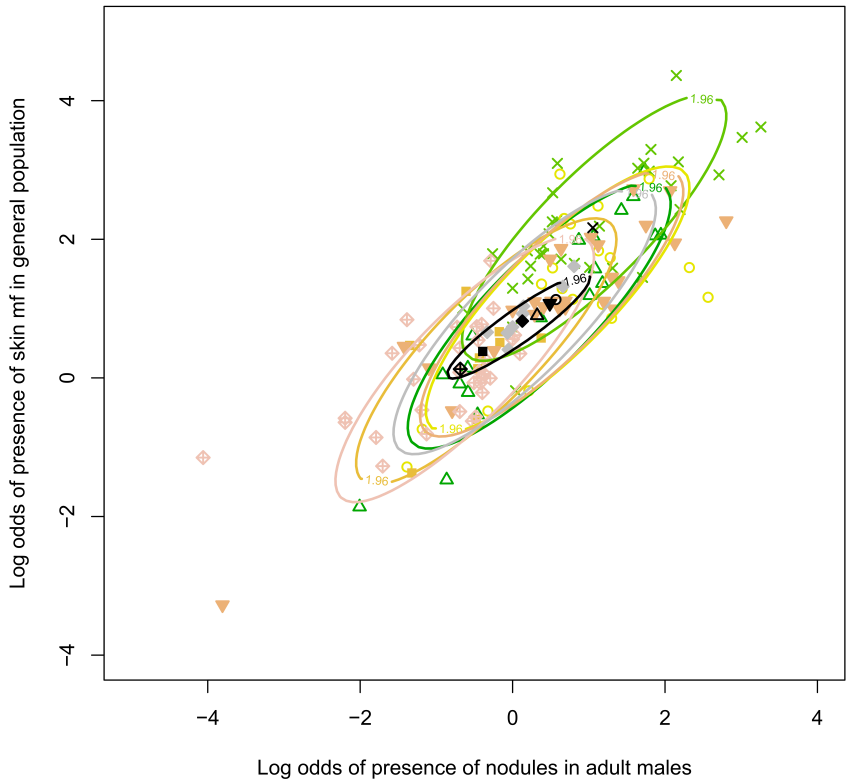

Figure 2.2: Association between prevalence of nodules in adult males and skin mf in the general population. Colored symbols represent data from seven geographical areas. Colored ellipses indicate the 95 % percentiles ($Z = 1.96$) of the predicted joint distributions of infection prevalences within each geographical area, based on the estimated variances and correlation of observations within geographical areas. Black symbols represent the mean infection prevalences in each of the geographical areas. The black ellipse represents the 95 % percentile of the joint distribution of mean infection prevalences in geographical areas, illustrating the deviating pattern in nodule and mf prevalence in Mbam, Cameroon (black and green crosshairs and upper right green ellipse). Predictions were based on a Bayesian hierarchical multivariate logistic regression model with a fixed effect for Mbam, Cameroon, and random effects for other geographical areas.

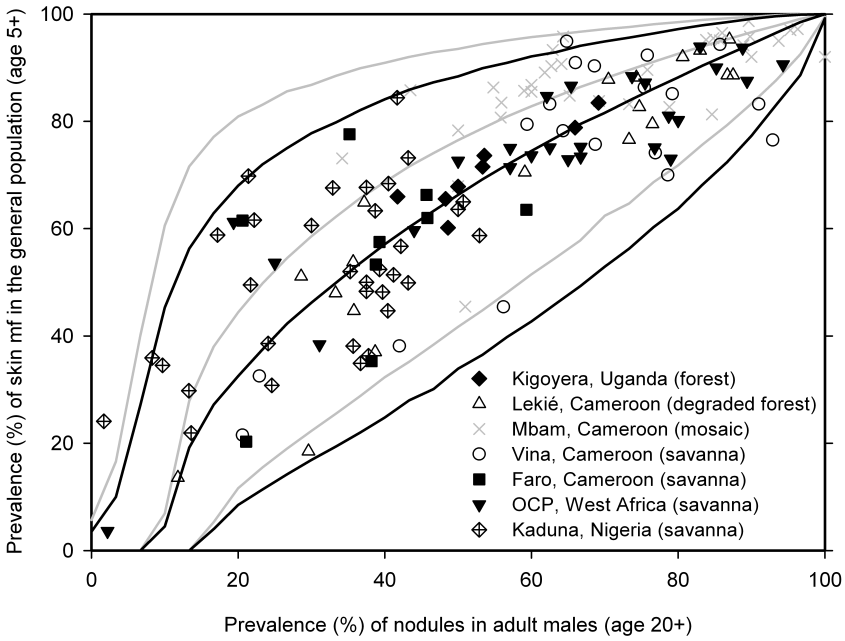

Figure 2.3: Predicted skin mf prevalence in the general population, given observed nodule prevalence in adult males. Symbols represent observed data by geographical area. Within each set of regression lines, the middle and outer lines relate to the median and 95 % Bayesian credible intervals of the posterior predictive distribution, respectively (black set for areas all areas but Mbam; grey set for Mbam, the only forest-savanna mosaic area). Predictions were made assuming that nodule prevalence was based on a sample of 30 adult males.

in the general population (aged ≥ 5 years). Our model is the first to examine geographical variation due to bioclime and other unmeasured variables, and to take account of measurement error in nodule prevalence. Our results show that there is a strong positive correlation between nodule and mf prevalence, but also significant variation between geographical regions, which should be taken into consideration when evaluating the prospects of elimination and the burden of disease. Our analysis showed significant geographical variation in patterns of nodule and mf prevalence, though not related to bioclimatic zones according to the classic forest vs. savanna

classification of onchocerciasis. In 'forest' areas – Lekié, Cameroon (degraded forest) and Kigoyera parish, Uganda (forest) – the patterns in nodule and mf prevalences did not differ much from the pattern in savanna areas. Yet, we found that mf prevalence levels in the general population were relatively higher in the only forest-savanna mosaic area (Mbam, Cameroon), while nodule prevalence in adult males levels were not significantly different. There are several possible explanations for this pattern. Most likely, the pattern in Mbam is explained by a different pattern in age-dependent exposure to black flies' bites. Both mf and nodule prevalences in individuals under the age of twenty years were relatively high in Mbam compared to the other areas in Cameroon, especially in villages with relatively low nodule prevalence in adult males (data not shown). This indicates that individuals in Mbam experience relatively high exposure levels at a young age. This might be explained by the presence of dense forest in this region with relatively few narrow open spaces, which is associated with higher dispersal of flies around the breeding sites (Le Berre et al. 1964). Therefore, exposure may not be concentrated near the breeding sites, but may extend over the whole village. Related to this, exposure may be less concentrated in adults (who frequently spent time near the breeding sites, forest galleries for fishing, etc.), but may be more equally distributed over all age groups. However, dense forest may not be unique for Mbam, and may also be present in other forest areas in our data set. Therefore, we can only say that it may be important to consider age-dependent patterns in exposure to black flies' bites and their effect on transmission when translating nodule prevalence data to mf prevalence. We rule out demography and survey methods, as all mf prevalences were standardized, the mean age of the sampled men from Mbam was similar to that of men from the other Cameroonian areas, methods for skin snipping and mf enumeration were the same as in other Cameroonian areas and, in addition, even conducted by the same person (MB performed all skin snipping in Faro, Lekié, and Mbam, and 50 % of skin snipping in Vina valley). Furthermore, it is also unlikely that the forest sites other than Mbam – Lekié and Kigoyera parish – harbor a savanna parasite strain (instead of the assumed forest parasite strain) as this is inconsistent with observed patterns

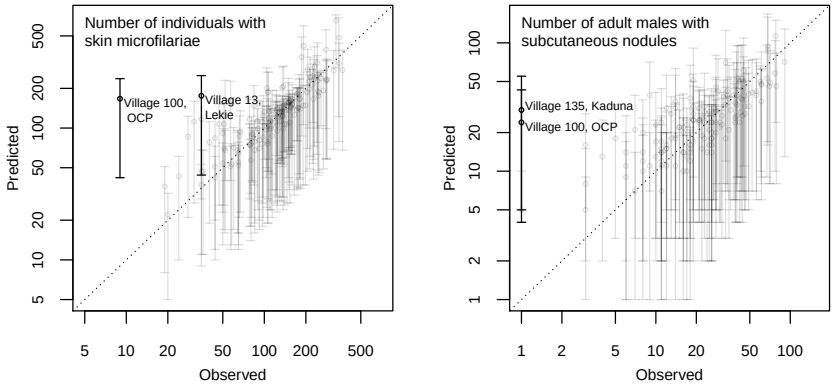

Figure 2.4: Comparison of observations (x-axis) versus model predictions (y-axis). The comparison was made by means of mixed posterior predictive checks of the numbers of individuals with detectable microfilariae in the skin and adult males with nodules. The dotted diagonal line represents the hypothetical perfect model fit. Error bars represent the 95 % Bayesian prediction interval for the numbers of adult males with nodules and individuals with detectable microfilariae in the skin each village, and should intersect with the diagonal line if the model fit is good.

of blindness in these areas (forest pattern) (Migliani et al. 1993; Babalola et al. 2011). Lastly, variation might have been caused by parasite characteristics not related to the classic subdivision into forest and savanna strains. Herder concluded that the parasite strains circulating in the Faro and Mbam areas were related but distinct from the strains from Vina and Lekié, based on phylogenetic linkage patterns (Herder 1994; Herder et al. 1994). However, this pattern was not confirmed by our analysis as the association between nodule and mf prevalence in Faro was very similar to the other areas but Mbam.

Our model could be used as a tool for assessing the prospects of elimination of onchocerciasis or the burden of onchocercal disease when pre-control nodule prevalence in adult males is the only measure of infection available (as is the case for most of Africa). With our model, an estimate of pre-control mf prevalence may be derived from pre-control nodule prevalence data. Such an estimate may be helpful for program planning, providing an indication of minimum

program duration (with regard to prospects of elimination), and could be helpful in the interpretation of ongoing epidemiological parasitological surveys that rely on the skin snipping method (in terms of progress towards elimination). Prospects of elimination may be evaluated by comparing the model-derived estimate of mf prevalence to known trends of infection levels in other foci with a similar history of mass treatment, or by means of dynamic modeling of the effect of mass treatments with ivermectin using onchocerciasis transmission models such as ONCHOSIM (Plaisier et al. 1990; Ngoumou and Walsh 1993; Plaisier et al. 1997) and others (Filipe et al. 2005; Poolman and Galvani 2006; Duerr, Raddatz, and Eichner 2011). Progress towards elimination could be evaluated by comparing current mf prevalences with model-derived estimates of precontrol mf prevalence and predicted trends in infection levels based on dynamical modeling. Likewise, the pre-control burden of ocular and dermal morbidity in endemic areas may be estimated based on literature data on the association between mf and disease prevalence (Dadzie et al. 1989; Remme et al. 1989; Dadzie et al. 1990). This would further allow assessment of the impact of control activities on population health, especially when combined with aforementioned dynamic models. If pre-control mf prevalence were to be severely underestimated or overestimated when derived from nodule prevalence data (due to measurement error and geographical variation), this may have important repercussions for the number of treatment rounds that is thought to be required to reach elimination, or the estimated burden of disease. Therefore, it is crucial to consider variation due to sample size and geographical variation in patterns of nodule and mf prevalence when doing this kind of assessment. Given the high level of variation and consequent uncertainty in the association between nodule and mf prevalence, translations should be made carefully and critically evaluated. We recommend that translations of village-level REMO data (based on samples of about 30 adult males) to mf prevalence are made based on the black lines in Figure 2.3 (which include uncertainty due to measurement error and geographical variation). In case of suspected high exposure of children to flies' bites, it may be more appropriate to apply the part of the model that mimics the observations in Mbam, Cameroon (grey lines in Figure 2.3). For

areas where infection prevalence is known to be homogeneously distributed, REMO samples from multiple villages could be pooled into a more precise estimate of pre-control nodule prevalence in the area, allowing more precise prediction of the pre-control mf prevalence. In Appendix A, section "Model application", we explain in more detail how our model should be applied to convert nodule prevalence to mf prevalence (e.g. how to make predictions for a group of villages).

In conclusion, we provide a tool to convert nodule prevalence in adult males to mf prevalence in the general population, which accounts for uncertainty due to measurement error and geographical variation. This tool allows interpretation of a large amount of pre-control data on levels of infection in Africa which may a) be combined with information on coverage of mass treatment to assess the feasibility of elimination of onchocerciasis and b) enable estimation of disease burden. Furthermore, we identified significant geographical variation in mf prevalence and nodule prevalence patterns that warrants further investigation of age-dependent transmission patterns of onchocerciasis.

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Chapter 3

Concurrence of dermatological and ophthalmological morbidity in forest type onchocerciasis

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Abstract

Prevalence of skin and eye disorders in African onchocerciasis (river blindness) is well documented. However, less is known about their joint occurrence. Information on concurrence may improve our understanding of disease pathogenesis and is required to estimate the disease burden of onchocerciasis. We analysed data from 765 individuals from forest villages in the Kumba and Ngambe Health districts, Cameroon. These data were collected in 1998, as baseline data for the evaluation of the African Programme for Onchocerciasis Control. Concurrence of symptoms was assessed using logistic regression. Onchocerciasis was highly endemic in the study population (63 % nodule prevalence among males aged ≥ 20). Considerable overall prevalences of onchocercal visual impairment (low vision or blindness: 4 %), troublesome itch (15 %), reactive skin disease (19 %), and skin depigmentation (25 %) were observed. The association between onchocercal visual impairment and skin depigmentation (OR 9.0, 95 % confidence interval: 3.9–20.8) was partly explained by age and exposure to infection (adjusted OR 3.0, 95 %-CI: 1.2–7.7). The association between troublesome itch and reactive skin disease was hardly affected by adjustment (adjusted OR 6.9, 95 %-CI: 4.2–11.1). Concluding, there is significant concurrence of morbidities within onchocerciasis. Our results suggest a possible role of host characteristics in the pathogenesis of depigmentation and visual impairment. Further, we propose a method to deal with concurrence when estimating the burden of disease.

Introduction

Onchocerciasis or river blindness is caused by the nematode *Onchocerca volvulus*. Infective larvae are transmitted between human hosts by the blackfly vector *Simulium* which breeds in river rapids. Adult female worms produce millions of larvae or microfilariae during their ten year lifespan (Duke 1993). These microfilariae migrate through the human body and cause deforming skin disease, severe itch and visual loss (Enk 2006). Onchocerciasis is endemic in large parts of sub-Saharan Africa. In Cameroon alone, at least 6.4 million people live in endemic areas that are currently subject to mass treatment with ivermectin (APOC 2009). Although there is ample information about the prevalence of onchocercal morbidity, we are aware of only one paper that explicitly describes concurrence of skin and eye disease in individuals. Browne reported that 42 % of subjects with onchocercal ocular lesions also suffered from skin depigmentation (DPM) compared to only four percent of all infected individuals (Browne 1960). It was not described whether similar overlap occurs between other ocular and skin manifestations; also, the biological mechanisms behind this concurrence were not clear.

In-depth analysis of data on concurrence may enhance our understanding of the pathogenesis of onchocerciasis. To date, it has been established that vision loss and blindness are most likely the result of progressive, cumulative tissue damage caused by microfilariae, as indicated by the increasing prevalence and incidence of ocular morbidity with age in stable endemic areas (Anderson et al. 1974a,b; McMahon et al. 1988; Burnham 1991; Little et al. 2004b). Further, onchocercal skin disease is thought to be partly mediated by genetic predisposition. For instance, a number of onchocercal skin manifestations have been linked to specific host immune responses (Rubio de Krömer, Medina-De la Garza, and Brattig 1995; Brattig 2004) and polymorphisms in genes encoding important parts of the human immune system (Brattig et al. 1986; Meyer et al. 1994; Murdoch et al. 1997; Hoerauf et al. 2002; Ali et al. 2007). However, the relative importance of cumulative exposure to infection and genetic predisposition in the development of morbidity is still unclear. Analysis of patterns in concurrence of morbidity may clarify this. For example, clustering of symptoms may occur in individuals with

the longest experience of infection, or heaviest infection load. Alternatively, history of infection and infection load may not explain concurrence very well, suggesting that genetic or behavioural factors play a role.

Information about concurrence of clinical manifestations is required for calculating the burden of disease in terms of DALYs (disability-adjusted life years) lost per year. DALY calculations preferably include all forms of morbidity that cause a significant loss of health at population level, either due to high severity or high prevalence. In the case of onchocerciasis, this means that symptoms of both skin and eye disease should be included. Of course, more than one type of symptom can be present in an individual. This is important because the loss of quality of life or life years due to a specific symptom may be influenced by the presence of another symptom. Therefore, simply calculating and summing the burden of disease for each separate symptom may lead to biased estimates of the overall burden of onchocerciasis-related morbidity in a population (Murray and Lopez 2000). For example, because individuals with onchocercal skin depigmentation are already stigmatised, the loss of quality of life from reactive skin disease due to onchocerciasis may be different than in otherwise healthy individuals. Knowledge about patterns in concurrence allows us to decide how to deal with such overlaps (also see Theory section).

In this study, data from a cross-sectional population survey in two forest areas of Cameroon were used to explore patterns in concurrence of four main types of onchocercal morbidity: skin depigmentation, reactive skin disease, severe itch and onchocercal visual impairment. Concurrence was quantified by means of logistic regression analysis, while adjusting for proxies for cumulative exposure to infection, in particular age and indicators of infection (presence of nodules and presence of microfilariae in the anterior chamber of the eye).

Materials and methods

Study sites

We performed a secondary analysis on data that were collected in 1998 as baseline data for the impact assessment study of the African Programme for Onchocerciasis Control (APOC). APOC performed surveys in ten sites, which all met predefined selection criteria: they were mesoendemic or hyperendemic for onchocerciasis as determined by earlier REMO studies ($> 20\,\%$ nodule prevalence in males ≥ 20 years old; Macé et al. 1997) and less than $25\,\%$ of the general population had received clinic-based treatment during the previous five years. For the current analysis we used data from two of the ten sites, which were considered sufficient for the purpose of the study. We used the data from two sites in Cameroon, which was a pragmatic selection, because these data were best documented and could be processed most easily.

The first study site was situated in the Health district of Ngambe in the Littoral Region. This district has about 100,000 inhabitants and is characterised by forest and the traversing River Sanaga. The study examinations were performed in July and August 1998, during the short dry season. The second study site was situated in the southwest province of Cameroon, in the Kumba Health District ($\sim$ 100.000 inhabitants). This district is characterised by tropical forest and has both a dry and a rainy season. Here, the examinations took place in November and December 1998 during the dry season. At both sites, Simulium squamosum is the only vector for transmission of onchocerciasis. A more detailed description of the study areas can be found elsewhere (Enyong et al. 2006).

Data collection

Prior to the surveys, a list of villages in each site was compiled. Next, a team of social scientists carried out a census of the population in the communities, starting in a given village, and progressing to the neighbouring ones until at least 1,500 persons were recorded in each site. Individuals aged five years and older were asked to present themselves for examination at a central point in the village for examination. In light of future evaluations of the APOC, a minimum

sample of 750 subjects per site was taken to be able to detect an absolute 10 % reduction in prevalence of onchocercal skin disease over time. Because ophthalmological examinations take longer than dermatological examinations and require more cooperation from the subject, only half of the individuals were examined ophthalmologically (every other individual of ten years or above).

Subjects who underwent examination were asked about their educational level. It was recorded whether subjects had followed – but not necessarily finished – secondary or primary education, or had followed none at all. Furthermore, each individual was questioned about symptoms typical of onchocerciasis. Severe itch was defined as itch associated with insomnia. Responses were marked as 'spontaneous' if information was volunteered and as 'prompted' if leading questions had to be asked. In the analysis, to avoid an underestimation of the prevalence of severe itch, spontaneous and prompted answers were merged. Finally, subjects were asked about the length of their stay in the village and whether they had used ivermectin, including frequency and time since last use. The dermatological examination was carried out in broad daylight, out of view of others. Onchocercal skin diseases were recorded on a standard protocol data entry form in accordance with a modified morphological classification of Murdoch et al. (1993). Reactive skin disease (RSD) was defined as acute papular onchodermatitis, chronic papular onchodermatitis and/or lichenified onchodermatitis. Skin microfilarial densities were not determined, because its measurement requires an invasive test, which was not considered ethical at the time given the primary objectives of the survey, which were surveillance and impact of mass treatment on morbidity. The dermatological data presented here have also been reported as part of the larger impact assessment study (Ozoh et al. 2011).

Visual acuity was measured by ophthalmic nurses using a standard Snellen illiterate 'E' chart. Final visual acuity was defined as the result obtained from the better eye with best correction (or pinhole if subject had no glasses and visual acuity $< 6/9$), and classified in accordance with the usual classes recommended by WHO: normal vision ($\geq 6/18$), low vision ($< 6/18$ but $\geq 3/60$) and blindness defined as the inability to count fingers at three metres ($< 3/60$; WHO

1980). Detailed eye examinations were carried out by an ophthalmologists (G.F. or B.N.), to establish the cause of reduced visual acuity per eye. Details of these procedures have been described before (Babalola et al. 2008; Umeh et al. 2010). In short, examination of the anterior segment was done after the subject had sat with the head bent down between the knees for at least two minutes, to allow microfilariae to emerge into the anterior chamber. The subject's eyes were then examined with a Haag Streit slit lamp biomicroscope ($\times$25 magnification). The posterior segment was examined after dilatation with tropicamide 1 % and/or phenylephrine 10 %, with direct and/or indirect ophthalmoscope. When more than one possible cause for the visual loss was detected (e.g. cataract and torpid uveitis), the examining ophthalmologists would have to assess and decide whether each cause was a primary, secondary (i.e. indirect) or minor cause for any visual loss of the same eye, based in clinical experience (e.g. cataract as primary cause, secondary to senychia from onchocercal uveitis). Low vision and blindness were defined as "onchocercal" if onchocercal lesions of the anterior or posterior segment of the eye were deemed the primary or secondary cause of ocular morbidity in at least one of the eyes.

All examining physicians were experienced in the field of onchocerciasis. For standardization of the examinations they were trained in advance. Further, during the survey physicians discussed frequently during the survey so that agreement on diagnoses was high.

Data management and statistical analysis

During the survey, separate standardised case report forms were used for the recording of ophthalmological and dermatological data. The forms were reviewed every evening. If there were inconsistencies, subjects were seen again the next day for re-examination. Data were entered in duplicate in SPSS Data Builder 4.0 at APOC headquarters, using a standardised entry form, and individual-level data from ophthalmological and dermatological examinations were merged. Inconsistencies due to typing errors were automatically detected and reviewed and corrected by reviewing the original hardcopy form. To enhance the representativeness of the sample for the local population

at risk of onchocercal morbidity, we excluded records of people who had stayed in the area less than three months. Most likely, these included records of recent immigrants and people visiting their relatives. Also, individuals for whom data was missing were excluded from the analysis. Further, because only very few people suffered from blindness, low vision and blindness were pooled in the analysis and will be referred to as 'visual impairment' from here onwards.

We assessed the association between skin depigmentation, RSD, severe itch and onchocercal visual impairment using a Venn diagram, odds ratios (ORs) and logistic regression. A Venn diagram is a graphical representation of the overlap of different groups (i.e. different symptoms) and was created with the Google Chart API[1]. Next, we compared the odds of having symptom A in persons negative for symptom B to the odds of having symptom A in persons positive for symptom B, while adjusting for the presence of symptoms C and D. An OR of 1.0 indicates that the concurrence of two symptoms is based on chance alone. To determine the relative importance of cumulative exposure to infection and host characteristics (genetic and behavioural factors) for the concurrence of symptoms, we corrected the ORs for cumulative exposure to infection. In the logistic regression model, cumulative exposure to infection was represented by two sets of variables: proxies for intensity of infection (presence of nodules and microfilariae in the anterior chamber of the eye, each taken separately) and proxies for duration of infection (age and age squared). Finally, the associations were additionally adjusted for gender, study site, educational level (three groups: any secondary, any primary, or no education at all) and ivermectin use (ever vs. never).

We performed sensitivity analyses with different definitions for morbidity (e.g. all-cause visual impairment versus onchocercal visual impairment). Sensitivity analyses were also performed in subsets of individuals with nodules, individuals who said they had or had not used ivermectin, and different cut-off values for time of stay in the area. Further, we checked to what extent our results were affected by regression towards the mean. In logistic and linear regression, it is

[1] https://developers.google.com/chart/image/docs/gallery/venn_charts, February 2010 release

assumed that there is no measurement error in the independent variables. However, there may be significant measurement error in the independent variable when it is an outcome itself (e.g. a symptom), leading to regression to the mean. In the case of logistic regression, this means that ORs will be biased towards one. Therefore, we repeated all analyses, but with swapped dependent and independent variables. All statistical analyses were performed in SPSS 15.0 for Windows.

Ethical clearance

The survey was carried out with approval of the Cameroon Ministry of Health. The survey was considered routine evaluation of a public health programme, and explicit approval of a medical ethical board was therefore not required. Oral informed consent was obtained from all participants or, in case of under-aged children, their parents or guardians. Individuals with any illness received free treatment or were referred to a nearby health facility, as appropriate. Before analysis, data were made anonymous to warrant privacy of patients.

Theory

Concurrence of morbidity is important for the Global Burden of Disease (GBD) project. The GBD project aims to inform health care policy makers about the magnitude and trends of disease and their causes, and is updated periodically. The main metric used in the GBD project is the disability adjusted life year (DALY), which is a measure of the future stream of healthy life lost as a result of the incidence of disease. This metric is the sum of the life years lost due to premature death and the loss in quality of life due to a symptom (Mathers, Ezzati, and Lopez 2007). The degree of loss of quality of life is determined by the disability weight assigned to a symptom. Disability weights range between zero and one, zero being equal to perfect health and one being equal to death. For instance, in the 2004 update of the GBD project (WHO 2004), the disability weight for blindness was 0.600. This means that for a blind individual with a remaining life expectancy of ten years (twenty years if he/she had not been blind), the DALY estimate would be the sum of six 'healthy

life years lost due to blindness' and the ten life years lost because of premature death due to blindness.

As illustrated in the introduction, the situation may become complicated when more than one symptom is simultaneously present in an individual: how should the disability weights be applied? So far, four methods have been suggested: the additive model, the multiplicative model, the maximum limit model and an approach based on separate disability weights for concurring conditions (Andrews, Sanderson, and Beard 1998; Mathers, Iburg, and Begg 2006; van Baal et al. 2006). The additive model simply adds up DALYs for different conditions and was used in the first Global Burden of Disease Study (Murray and Lopez 1996). However, this model may give biased results as the individual burden due to a symptom may be modified by the presence of a second symptom (Murray and Lopez 2000). This is particularly clear when the symptom-specific disability weights add up to a value above 1: the total disability should by definition be between 0 (reflecting the best possible health state) and 1 (reflecting the worst possible health state or equating death). In contrast, the multiplicative model assumes that a second condition increases the burden of disease, but proportional to the 'remaining' quality of life which is left after subtracting the burden of the first condition. This way, the compound disability weight is always between zero and one. For instance, an individual with e.g. both symptom A (disability weight 0.3) and symptom B (disability weight 0.4) would be assigned a compound disability weight of 0.58 $(1 - ((1 - 0.3) * (1 - 0.4)))$. This model was applied in the Australian Burden of Disease project (Mathers, Vos, and Stevenson 1999). Next, there is the maximum limit model, which simply assumes that the burden of disease in an individual is determined by the worst condition present. Last, there is the approach that uses separate disability weights for every combination of conditions. Here, the drawback is that determining disability weights for many combinations of conditions may be cumbersome and unfeasible.

Results

At the time of investigation, 1,520 and 855 individuals were examined dermatologically and ophthalmologically, respectively . After exclusion of individuals who lived in the village for less than three months ($N = 117$ and 75), merged ophthalmologic and dermatologic data was available for 765 individuals: 427 in Kumba district and 338 in Ngambe district. These samples consisted of 52 % and 46 % males, respectively. The age distribution differed considerably, with 48 % and 34 % being under 30, respectively (Table 3.1). In both study sites, about a quarter of the examined population had not followed any formal education. However, more people in Ngambe than in Kumba had had secondary education. In Kumba, 29 % of eligible subjects reported use of ivermectin at some point in time. In Ngambe, this was 49 % of the subjects. Overall, onchocerciasis was highly endemic as indicated by the nodule prevalence in adult males (age ≥ 20) of §62% at the Kumba site and 66 % at the Ngambe site. The overall nodule prevalence increased with age (Figure 3.1) and was higher in males than females (56 % vs. 44 %).

Overall and site specific prevalences of morbidity are shown in Table 3.2, standardised to the total study population by age and sex. Skin depigmentation (DPM) was the most prevalent dermatological diagnosis (25 %) and became more prevalent with age (Figure 3.1). In nearly all cases, DPM was located on the lower limbs ($N = 192/193$). In 132 cases DPM had advanced to a stage with spots of complete pigment loss. In the other 60 cases, DPM was less severe (yellow-brown spots). Reactive skin disease (RSD) was also highly prevalent in the study population (19 %; Table 3.2). However, the prevalence of RSD did not show an increasing pattern after age 30 (Figure 3.1) and neither did any of the sub-diagnoses (acute papular, chronic papular and lichenified onchodermatitis; data not shown). Spontaneously mentioned severe itch was prevalent in both study sites. In addition, a large number of subjects said they suffered from severe itching after being prompted. For instance, 3.2 % of all Ngambean men and 4.4 % of Ngambean women spontaneously mentioned severe itch. When prompted, an additional 4.5 % of men and 3.8 % of women said they suffered from severe itch.

Unlike the prevalence of nodules, the prevalence of microfilariae

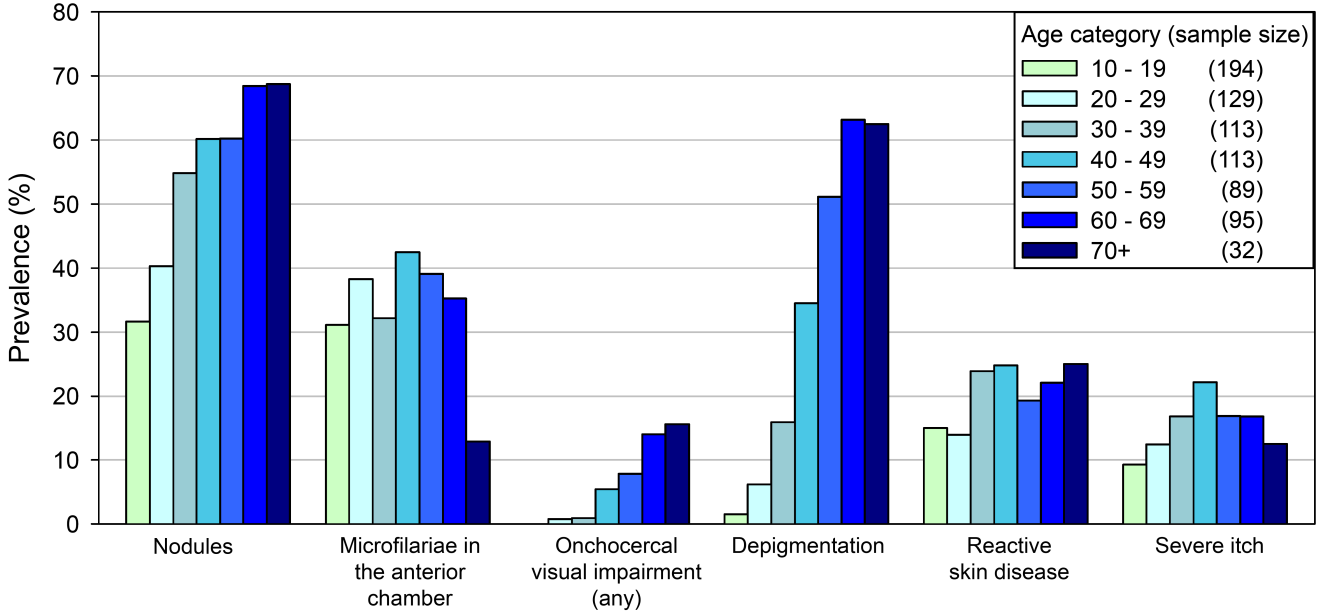

Figure 3.1: Distribution of onchocercal morbidity and measures of infection over age categories ($N = 765$). Onchocercal visual impairment includes low vision and blindness.

Table 3.1: Study population characteristics per site.

	Kumba $N = 427$		Ngambe $N = 338$		Total $N = 765$	
	n	%	n	%	n	%
Male gender	222	52.0	156	46.2	378	49.4
Age						
10–19	120	28.1	74	21.9	194	25.4
20–29	87	20.4	42	12.4	129	16.9
30–39	68	15.9	45	13.3	113	14.8
40–49	60	14.1	53	15.7	113	14.8
50–59	40	9.4	49	14.5	89	11.6
60–69	41	9.6	54	16.0	95	12.4
≥ 70	11	2.6	21	6.2	32	4.2
Education						
None	115	26.9	79	23.4	194	25.4
Primary	268	62.8	171	50.6	439	57.4
Secondary	44	10.3	86	25.4	130	17.0
Uknown	0	0.0	2	0.6	2	0.3
Nodule(s) present	197	46.1	150	44.4	380	49.7
Unknown	0	0.0	2	0.6	2	0.3
Ivermectin use (ever)	124	29.0	166	49.1	290	37.9

in the anterior chamber was not associated with age (Figure 3.1). After direct standardisation for age and gender (Table 3.2), the prevalence of onchocercal visual impairment was higher in Kumba (6.9 %) than in Ngambe (2.8 %). In contrast, after standardisation, the prevalence of onchocercal blindness alone was similar in both study sites (Kumba 2.0 %; Ngambe 1.4 %).

Figure 3.2 depicts the prevalence of the main morbidities and their joint prevalences in a graphical fashion. For instance, DPM was observed in 190 individuals ($112 + 24 + 16 + 14 + 13 + 6 + 3 + 2$) of whom 25 also suffered from onchocercal visual impairment ($14 + 6 + 3 + 2$). Only eight individuals had onchocercal visual impairment but no DPM. The question remains – can the observed overlap in prevalences be attributed to chance alone? Table 3.3 reports the concurrence of morbidities, expressed in odds ratios. Visual impairment and DPM concurred more often than may be expected based on chance alone (odds ratio 9.0, 95 % confidence

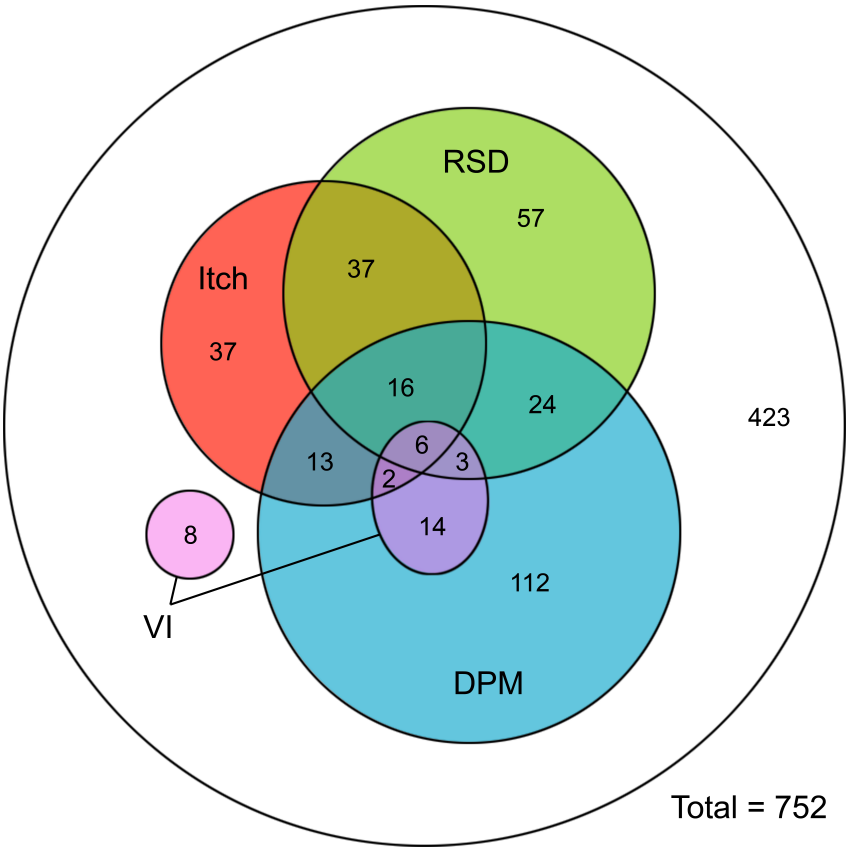

Figure 3.2: Graphical representation of concurrence of onchocercal morbidity (Venn diagram). RSD: reactive skin disease ($N = 143$); Itch: severe itch ($N = 111$); DPM: depigmentation ($N = 194$); VI: onchocercal visual impairment (including low vision and blindness, $N = 33$). The surface of each circle and the overlap between any combination of circles is approximately proportional to the size of the population it represents. The outer circle represents the study population ($N = 752$). The blank area within the outer circle represents individuals without RSD, DPM, VI and itch ($N = 423$).

Table 3.2: Prevalence of morbidity per site standardised to the total study population by age and sex.

	Kumba %	Ngambe %	Total n/N[a]	%
Reactive skin disease[b]	21.7	18.3	148/763	19.4
APOD[c]	10.9	9.0	76/763	10.0
CPOD[d]	9.9	12.6	77/763	10.1
LOD[e]	5.8	1.1	27/763	3.5
Depigmentation	29.8	20.7	193/763	25.3
Severe itch[f]	21.4	7.4	113/765	14.8
MFAC[g]	44.0	24.1	262/752	34.8
Visual impairment[h]				
All cause	8.7	6.6	56/754	7.4
Onchocercal[i]	6.9	2.8	33/754	4.4
Blindness[h]				
All cause	2.6	3.3	24/754	3.2
Onchocercal[i]	2.0	1.4	13/754	1.7

[a] When a record was unclear about presence of a given symptom, the individual was excluded.
[b] Presence of either APOD, CPOD and/or LOD.
[c] Acute papular onchodermatitis.
[d] Chronic papular onchodermatitis.
[e] Lichenified onchodermatitis.
[f] Reported spontaneously or when prompted.
[g] Microfilariae in the anterior chamber of either eye.
[h] Normal vision = best corrected visual acuity of $\geq 6/18$ in the best eye; visual impairment = best corrected visual acuity of $< 6/18$, including blindness; blindness = best corrected visual acuity $< 3/60$ in the best eye.
[i] Onchocerciasis was a primary or secondary cause of pathology in the anterior or posterior compartment of either eye.

interval: 3.9–20.8). This association decreased by half but remained significant after adjustment for cumulative exposure to infection (OR 3.0, 95 %-CI: 1.2–7.5) and the remaining covariables (OR 3.0, 95 %-CI: 1.2–7.7). Further, severe itch was associated with RSD (OR 7.5, 95 %-CI: 4.8–11.7). This association hardly changed after adjustment for any of the covariables. We found one more association of borderline significance between RSD and DPM. However, this association disappeared after correction for exposure to infection. Severe itch and RSD were not associated with onchocercal visual

impairment.

In the sensitivity analysis, the association between DPM and onchocercal visual impairment decreased only slightly when visual impairment from any cause was considered or when uncorrected measures of visual acuity were used (including refractive errors) (data not shown). Separate analyses of the subsets of subjects with nodules or those who had or had not used ivermectin at some point in time, did not yield different results (data not shown). Likewise, duration of stay in the area did not significantly influence the results (data not shown). Exchanging the places of the predicted symptom (i.e. dependent variable) and another symptom in the model (independent variable) influenced the ORs only marginally (± 0.1).

Discussion

We explored concurrence of onchocercal morbidity in a hyperendemic rainforest area of Cameroon. We found that onchocercal visual impairment (including low vision and blindness) and depigmentation (DPM) concurred significantly. This association was partly attributable to cumulative exposure to infection. Reactive skin disease (RSD) and severe itch also concurred often. This association could not be explained by cumulative exposure to infection. Further, the association between DPM and RSD was completely attributable to cumulative exposure to infection. We did not find any negative associations between disease entities. The study population was selected via voluntary participation instead of random sampling. The middle-aged were underrepresented in the study population (most likely related to work) and the elderly are overrepresented, which is reflected in the age distribution of the study population. It is possible that people with multiple symptoms were overrepresented because they were more willing to come to the central point for examination. This may have amplified the estimate of concurrence, especially for visual impairment and DPM. However, the observed patterns in concurrence fit the biology of onchocerciasis and can hardly be explained by a selection bias only. Therefore, even though our estimates may be somewhat inflated, they are an adequate illustration of patterns in concurrence.

We estimated to what extent concurrence could be explained by cumulative exposure to infection. Our results show that DPM and onchocercal visual impairment concur more often at the individual level than may be expected based on chance alone. This pattern was at least partly mediated through individuals' levels of cumulative exposure to infection, age being the most important factor. However, our proxy measures for cumulative exposure to infection (age, nodule prevalence and microfilariae in the anterior chamber) may not fully account for the present and past exposure to microfilariae. Better indicators of cumulative infection intensity, such as skin mf counts at present and several moments in the past, would perhaps explain a larger part of the concurrence. For now, we cannot exclude that other personal factors also predispose individuals to the development of DPM and visual impairment. For instance, the HLA-DQ alleles associated with DPM16 might also increase the risk of onchocercal visual impairment. Alternatively, DPM may be (partly) mediated by the same auto-immune mechanisms that are associated with onchocercal disease of the posterior segment of the eye (McKechnie et al. 1993; McKechnie et al. 2002). From the observed age patterns, we can deduce that DPM probably occurs before the onset of visual impairment.

Although it has been shown that there is a strong association between onchocercal itch and RSD (Makunde et al. 2000; Murdoch et al. 2002), the biological mechanisms behind the two are still unclear. It has been shown that histamine, a mediator for itch (Rees and Murray 2005), can be induced by onchocercal antigens (González-Muñoz et al. 1999). However, we are not aware of any reports on the direct immunological relation between RSD and severe itch. In our study, individuals with RSD were also more likely to suffer from severe itch. This association could not be explained by cumulative exposure to infection, probably because of the relatively acute and intermittent nature of troublesome itch. Because RSD and itch occur in the same organ system, our observations imply a causal relation between the two. Most likely, both are triggered by recognition of antigens from living and/or degrading microfilariae by the host immune system. Further, DPM concurred to some extent with RSD. However, this pattern was entirely attributable to

Table 3.3: Concurrence of onchocercal morbidity. Numbers represent odds ratios (OR) and 95 % confidence intervals (95 %-CI) from three logistic regression models (dependent variables are onchocercal visual impairment, reactive skin disease and depigmentation respectively). Because of missing data in 35 individuals, 730 of 765 subjects (95 %) were included in these analyses.

Concurrent morbidity (dependent vs indepentent)			Odds ratio (95 %-CI)		
			Crude[a]	Adjusted for exposure to infection[b]	Adjusted for all covariables[c]
Onchocercal VI[d]	vs	Severe itch	1.7 (0.7–4.4)	1.5 (0.5–4.5)	1.4 (0.5–4.3)
Onchocercal VI[d]	vs	Reactive skin disease	1.0 (0.4–2.6)	1.0 (0.4–2.8)	1.1 (0.4–3.3)
Onchocercal VI[d]	vs	Depigmentation	9.0 (3.9–20.8)[e]	3.0 (1.2–7.5)[f]	3.0 (1.2–7.7)[f]
Reactive skin disease	vs	Severe itch	7.5 (4.8–11.7)[e]	7.1 (4.5–11.1)[e]	6.9 (4.2–11.1)[e]
Reactive skin disease	vs	Depigmentation	1.5 (1.0–2.3)[g]	1.3 (0.8–2.2)	1.3 (0.7–2.2)
Depigmentation	vs	Severe itch	0.8 (0.5–1.2)	1.0 (0.6–1.8)	0.8 (0.4–1.5)

[a] Adjusted for presence of other morbidity (onchocercal visual impairment, reactive skin disease, depigmentation and severe itch).

[b] Adjusted for presence of other morbidity, age, age^2, presence of nodules and presence of microfilariae in the anterior chamber of the eye.

[c] Adjusted for presence of other morbidity, age, age^2, gender, educational level, study site, presence of nodules, presence of microfilariae in the anterior chamber of the eye and ivermectin use (ever).

[d] Visual impairment: best corrected visual acuity of $< 6/18$, including blindness with onchocerciasis as main or secondary cause of pathology in the anterior or posterior compartment of either eye.

[e] p-value < 0.0001

[f] p-value < 0.05

[g] p-value < 0.1

cumulative exposure to infection. This fits the idea that RSD and DPM are part of a continuum of onchocercal skin manifestations, which may be simultaneously present and evolve into one another (Murdoch et al. 1993).

In previous updates of the Global Burden of Disease project, estimates of the burden of onchocerciasis only took blindness, visual impairment and itch into account (Remme 2004; Mathers, Ezzati, and Lopez 2007). However, because skin disease composes most of the burden of onchocerciasis in forest areas (Murdoch 2010), new estimates of the burden of disease should also include RSD and DPM. However, the different types of onchocercal skin disease exert their burden via similar mechanisms, namely stigma and low self-esteem due to skin disfigurement (WHO 1995; Alonso, Murdoch, and Jofre-Bonet 2009). Therefore, if a person is already stigmatised because of one skin condition, then the presence of an additional skin condition does not necessarily confer additional stigma. Our results indicate that in forest areas where onchocerciasis is endemic, there is considerable concurrence of DPM and RSD. This overlap should be taken into account in future calculations to avoid an overestimation of the burden of onchocerciasis. Similar issues may arise when estimating the burden of other neglected tropical diseases which involve a variety of symptoms, like schistosome infections (van der Werf et al. 2003).

In the literature, several methods are suggested to take account of concurrent morbidity when estimating the burden of disease (Andrews, Sanderson, and Beard 1998; Mathers, Iburg, and Begg 2006; van Baal et al. 2006). Preferably, the choice of model depends on the performance of such a model for a given disease. For instance, in a Canadian population-based study, the multiplicative model has been shown to work well for a large number of concurring chronic conditions (Flanagan et al. 2006). In another study, the performance of the additive, multiplicative and maximum limit models was tested for injuries and comorbidity of different severities in the Netherlands (Haagsma et al. 2011). The authors concluded that the additive and multiplicative models performed well, in contrast to the maximum-limit model. For all three models performance was best in case of severe comorbidity and worse in case of mild to moderate

comorbidity. A possible explanation was that individuals suffering from mild to moderate comorbidity might have adapted differently to their injuries than those suffering from severe comorbidity, leading them to value their health states differently. In view of this, it does not seem straightforward to say that one model is always the best; rather, the performance depends on the context of the health conditions under consideration. Unfortunately, the performance of the aforementioned models has yet to be evaluated for onchocerciasis and other neglected tropical diseases. Until then, rather than choosing a model based on performance, we propose a pragmatic approach.

For the calculation of DALYs due to onchocerciasis, we propose that separate estimates are made for the following three groups of symptoms. The first group concerns deforming skin disease (RSD and DPM). Considering the similar mechanisms of conferring burden in this group (stigma and low self-esteem), overlapping symptoms can be taken into account by only counting the symptom with the greatest disability weight in a given individual. The other two groups of symptoms are troublesome itch and visual impairment. In the latter, separate disability weights for low vision and blindness can be used because, according to the WHO criteria (WHO 1980), these diagnoses are mutually exclusive. Making two assumptions, we argue that the DALY estimates for deforming skin disease, troublesome itch and visual impairment may be added up without causing a gross over- or underestimation of the global burden of onchocerciasis. The first assumption is that each of the three categories involves a different mechanism of imposing a burden on an individual (i.e. stigmatisation, discomfort and reduced visual acuity). Therefore, if symptoms of different classes are simultaneously present in an individual, that person's total burden of disease is probably very close to the sum of burdens of all classes of symptoms (e.g. skin disfigurement and itch). Of course, the maximum possible disability weight should not exceed one. However, this would be unlikely to happen because the sum of the disability weights for blindness (0.600) troublesome itch (0.068; Mathers, Ezzati, and Lopez 2007) and disfiguring skin disease would probably be far under one. The second assumption concerns the effect of simultaneous presence of

symptoms on the total DALY estimate for a population. We argue that this effect is limited when the burden is calculated for the proposed three groups because either the prevalence of a group of symptoms is very low compared to another and/or the concurrence of groups of symptoms is very low (e.g. visual acuity and itch).

In conclusion, there is significant concurrence of different types of morbidity in onchocerciasis. We show a possible way of dealing with concurrence when estimating the burden of disease. Clustering of DPM and visual impairment could only be partly explained by exposure to infection, suggesting a possible role for individual susceptibility in disease pathogenesis.

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Chapter 4

African Programme for Onchocerciasis Control 1995–2015: model-estimated health impact and cost

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Abstract

Onchocerciasis causes a considerable disease burden in Africa, mainly through skin and eye disease. Since 1995, the African Programme for Onchocerciasis Control (APOC) has coordinated annual mass treatment with ivermectin in 16 countries. In this study, we estimate the health impact of APOC and the associated costs from a program perspective up to 2010 and provide expected trends up to 2015. With data on pre-control prevalence of infection and population coverage of mass treatment, we simulated trends in infection, blindness, visual impairment, and severe itch using the micro-simulation model ONCHOSIM, and estimated disability-adjusted life years (DALYs) lost due to onchocerciasis. We assessed financial costs for APOC, beneficiary governments, and non-governmental development organizations, excluding cost of donated drugs. We estimated that between 1995 and 2010, mass treatment with ivermectin averted 8.2 million DALYs due to onchocerciasis in APOC areas, at a nominal cost of about US$257 million. We expect that APOC will avert another 9.2 million DALYs between 2011 and 2015, at a nominal cost of US$221 million. Our simulations suggest that APOC has had a remarkable impact on population health in Africa between 1995 and 2010. This health impact is predicted to double during the subsequent five years of the program, through to 2015. APOC is a highly cost-effective public health program. Given the anticipated elimination of onchocerciasis from some APOC areas, we expect even more health gains and a more favorable cost-effectiveness of mass treatment with ivermectin in the near future.

Introduction

Onchocerciasis is caused by *Onchocerca volvulus*, a filarial nematode restricted to human hosts. The adult female worms reside in subcutaneous nodules where they produce millions of microfilariae during their on-average ten-year life span (Duke 1993). The microfilariae are found predominantly migrating through the skin and eyes and are transmitted by biting flies of the genus *Simulium* (the vector), an obligatory part of the parasite's life cycle. Onchocerciasis is responsible for a considerable burden of disease, mainly because of visual impairment, blindness, disfiguring skin lesions, and severe itching, which are the results of continuous exposure to microfilariae. Most of the global burden of onchocerciasis ($> 99\,\%$) is found in sub-Saharan Africa. In the West African savanna, where onchocerciasis is of a severely blinding form (savanna type), fear of blindness previously led to abandonment of fertile river basins. However, by now, onchocerciasis has been largely eliminated from West Africa by the Onchocerciasis Control Programme (1974–2002), which relied on intense vector control and mass treatment with the drug ivermectin (Boatin 2008).

In the more central and eastern parts of Africa, where onchocerciasis is usually of the less blinding form (forest type), there was no control or control only at a limited scale until the inception of the African Programme for Onchocerciasis Control (APOC) in 1995. APOC is a morbidity control program scheduled to be active until 2015, requiring that by that year, participating countries support and coordinate control measures independently. Since 1995, APOC has mapped infection with *O. volvulus* in 20 countries (Noma et al. 2002) and has coordinated interventions in 16 countries where onchocerciasis is considered a public health problem (Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Liberia, Malawi, Nigeria, South Sudan, Sudan, Tanzania, and Uganda), covering endemic areas inhabited by about 71.5 million people in 1995. APOC's main strategy is to implement annual mass treatment with ivermectin.

Ivermectin kills microfilariae and permanently reduces the production of microfilariae by adult female worms, slowing down transmission and preventing morbidity (Plaisier et al. 1995; Basáñez

et al. 2008). Annual mass treatment with ivermectin is implemented through a community-directed treatment approach, empowering communities to take responsibility for ivermectin delivery and to decide how, when, and by whom ivermectin treatment is administered. Mass treatment with ivermectin is enabled by donation of the drug by the pharmaceutical company Merck through the Mectizan Donation Program. Furthermore, coordination of the program is funded by donor countries (through the World Bank) and national onchocerciasis task forces (including beneficiary governments and non-governmental development organizations). To demonstrate APOC's importance, validate the efforts of endemic communities and national task forces, and maintain commitment of all stakeholders, it is essential to establish the health impact and cost of APOC.

Here, we present the estimated impact of APOC on population health and the costs involved up to 2010, with extrapolated trends up to 2015. An impact assessment would ideally be based on observed trends of infection and morbidity, but such longitudinal data are of limited availability in APOC areas. We therefore estimated trends of infection and morbidity based on APOC data of pre-control levels of infection and history of mass treatment, and literature-derived associations between infection and morbidity and the effect of treatment on infection and morbidity. For our calculations, we used ONCHOSIM, an established microsimulation model for transmission and control of onchocerciasis (Plaisier et al. 1990, 1997).

Methods

Project-population by endemicity category and project-specific history of control

The impact of APOC was estimated at project level (a project being an implementation unit for mass treatment with ivermectin), while taking account of the prevailing type of onchocerciasis (i.e. savanna versus forest or mixed forest/savanna, with different patterns of morbidity) and the project-specific history of control. Project populations were further stratified by endemicity groups, to take account of differences in the pre-control prevalence of morbidity (which

is non-linearly associated with infection) and the potential impact of mass treatment (e.g. the impact is relatively lower in highly endemic areas due to more residual transmission between treatment rounds). We considered four endemicity levels: non-endemic (prevalence of onchocercal nodules in adult males $< 1\,\%$), hypoendemic (nodule prevalence $\geq 1\,\%$ and $< 20\,\%$), mesoendemic (nodule prevalence $\geq 20\,\%$ and $< 40\,\%$), and hyperendemic (nodule prevalence $\geq 40\,\%$).

We estimated the size of the population at risk for infection in the 107 geographical project areas covered by APOC, for the years 1995–2010 (see Appendix B). These estimates were based on records kept by community-appointed drug distributors, aggregated to the project level. From the same data, we took the reported number of individuals who were treated with ivermectin during mass treatment (Appendix B) and calculated the average therapeutic coverage of mass treatment in each project per calendar year (i.e. the fraction of the population at risk that was treated). Based on data from extensive pre-control mapping studies, we estimated the fraction of the population in the different endemicity categories and the mean pre-control infection level in each endemicity category (Appendix B).

For the years 2011–2015, we assumed that population size will increase according to the latest known national growth rate (as reported by the United Nations World Population Prospects, published 11 May 2010, accessed 24 October 2011). If therapeutic coverage in 2010 was already at or above 75 %, we assumed that coverage in the years 2011–2015 will remain equal to that in 2010. For those few project in which this was not yet the case, we assumed that between 2011 and 2015, therapeutic coverage will be scaled up by 10 percentage points per year (conservative compared to reported coverage patterns in projects that started mass treatment between 1995 and 2010), to a maximum of 75 % (conservative compared to the longest-running projects that reported stable coverage levels around 80 % in 2008–2010).

Simulating trends in infection and morbidity

For each unit of analysis (project, onchocerciasis type, endemicity), we simulated trends in infection, morbidity, and mortality in

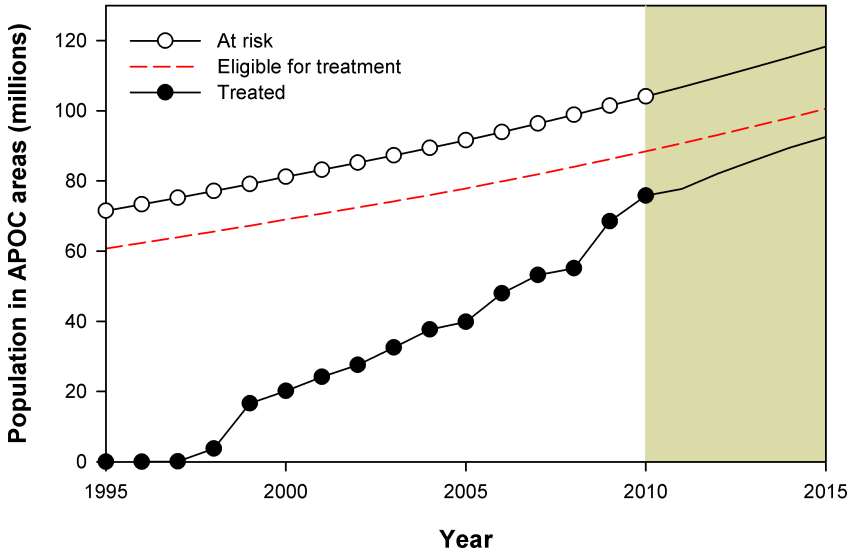

Figure 4.1: Population at risk and treated in areas covered by the African Programme for Onchocerciasis Control. Dots represent time points for which data were available; projections for 2011–2015 (shaded area) are based on the assumptions that populations continue to grow according to the latest known growth rates and that all projects scale up therapeutic coverage by 10 percentage points per year (up to a maximum coverage of 75 %).

the ONCHOSIM model (Plaisier et al. 1990; Habbema, van Oortmarssen, and Plaisier 1996; Plaisier et al. 1997), considering the project-specific history of mass treatment (Appendix B). For each endemicity stratum, ONCHOSIM was calibrated so that it could reproduce the average pre-control level of infection (Appendix B). Furthermore, ONCHOSIM was calibrated to reproduce the association between the prevalence of infection and morbidity (visual impairment, blindness, and itch) as estimated by analysis of literature data (Appendix B). Based on previous studies with ONCHOSIM, we assumed that ivermectin instantly kills all microfilariae and permanently reduces the capacity of adult female worms to release microfilariae by 35 % in treated individuals (with cumulative effects for repeated treatments) (Plaisier et al. 1995, 1997). Individual participation in mass treatment was assumed to depend on age, sex

(pregnant women and children under the age of five were assumed to be excluded from treatment), random non-compliance (i.e. temporal factors), and systematic non-compliance (i.e. fixed individual factors other than age and sex e.g. inclination towards participation). Systematic non-compliance was assumed to play a larger role when overall treatment coverage was lower (i.e. when there is lower inclination to participate in general), and vice versa (Plaisier et al. 1990; Habbema, van Oortmarssen, and Plaisier 1996). No simulations were performed for hypoendemic areas, as ONCHOSIM predicts that transmission of infection is unsustainable without migration of infected flies and/or human, and information on migration was lacking. Instead, we assumed that the prevalence of infection and morbidity in hypoendemic areas was 1/3 of that in mesoendemic areas, both pre-control and during control. For non-endemic areas, we assumed that prevalence of infection and morbidity was always zero.

Calculating the health impact

We combined the predicted trends in prevalence of infection, morbidity, and mortality with information on the number of people at risk, yielding an estimate of the absolute number of cases of infection, morbidity, and deaths in each stratum. After aggregation of these results over all APOC projects, we calculated the burden of disease in terms of disability-adjusted life years (DALYs), which in our case is the sum of years lived in disability due to troublesome itch, visual impairment, and blindness, weighted by the loss of quality of life due to each symptom: 0.068, 0.282, and 0.594, respectively (WHO 2004); and years of life lost due to excess mortality from blindness (Appendix B). Every incident case of blindness was attributed 8 years of life lost, based on the average age of onset of blindness in ONCHOSIM, the associated lifeexpectancy (16 years) of a healthy person of the same age, and an estimated 50 % reduction in remaining life-expectancy due to blindness (Appendix B). The estimated annual burden of disease was compared to the burden in a counterfactual scenario in which the pre-control prevalence of infection and morbidity did not change (i.e. as if there were no mass treatment), yielding an estimate of the averted disease burden. All DALY

estimates in the present study are undiscounted.

Sensitivity analysis

We assessed the influence of uncertain model assumptions on the estimated health impact, by means of univariate and multivariate sensitivity analyses (Appendix B). In a univariate sensitivity analyses, we assumed extreme, though plausible parameter values for each of the selected parameters. In a multivariate sensitivity analysis, the analysis was repeated, based on 200 sets of random parameter values. Parameter values were randomly drawn from triangular distributions with modes equal to the values used in the main analysis, and minimum and maximum values equal to those used in the univariate sensitivity analyses. To arrive at a crude estimate of the uncertainty in the estimated health impact, the results of the multivariate sensitivity analysis were expressed as the 2.5^{th} and 97.5^{th} percentiles of results from 200 repeated analyses.

Estimating the cost of APOC

We estimated the financial costs for coordination of ivermectin mass treatment taken on by APOC and national onchocerciasis task forces (beneficiary governments and non-governmental development organizations), based on APOC financial reports for The World Bank, which acts as fiscal agent for APOC. Because governments of beneficiary countries will eventually have to finance and coordinate ivermectin mass treatment, costs were estimated from a program perspective, not accounting for community costs and costs of donated drugs. For the years 1995–2003 and 2010, cost data for national onchocerciasis task forces were not available and were assumed to be proportional to APOC expenditures by a factor based on data available for other years. Expenditures for 2011–2015 were estimated based on the expected number of treatments in that period multiplied by the estimated cost per treatment in 2010. All costs are reported in nominal values, by which we mean that the presented costs are the amounts that were actually spent (i.e. uncorrected for inflation, and undiscounted).

Table 4.1: Size and distribution of population in APOC target areas (thousands and percentage of total). Populations were stratified by onchocerciasis type, endemicity class and the history of mass treatment. The history of mass treatment is expressed as the number of treatment rounds provided through 2010.

Onchocerciasis type	Endemicity class	Number of treatment rounds provided through 2010								Total	
		1–2		3–5		6–9		10–13			
Forest/mixed	Non-endemic	3	0.0%	129	0.1%	119	0.1%	342	0.3%	593	0.6%
	Hypoendemic	155	0.1%	5,669	5.4%	5,245	5.0%	14,170	13.6%	25,239	24.3%
	Mesoendemic	71	0.1%	4,179	4.0%	4,210	4.0%	11,768	11.3%	20,228	19.4%
	Hyperendemic	13	0.0%	4,128	4.0%	5,428	5.2%	15,201	14.6%	24,770	23.8%
	Total	243	0.2%	14,104	13.6%	15,002	14.4%	41,481	39.9%	70,831	68.1%
Savanna	Non-endemic	0	0.0%	1	0.0%	1	0.0%	18	0.0%	19	0.0%
	Hypoendemic	0	0.0%	871	0.8%	1,048	1.0%	12,837	12.3%	14,756	14.2%
	Mesoendemic	0	0.0%	1,695	1.6%	1,143	1.1%	9,402	9.0%	12,240	11.8%
	Hyperendemic	0	0.0%	1,900	1.8%	255	0.2%	4,049	3.9%	6,203	6.0%
	Total	0	0.0%	4,467	4.3%	2,446	2.4%	26,306	25.3%	33,219	31.9%
Grand Total		243	0.2%	18,571	17.8%	17,449	16.8%	67,787	65.1%	104,050	100.0%

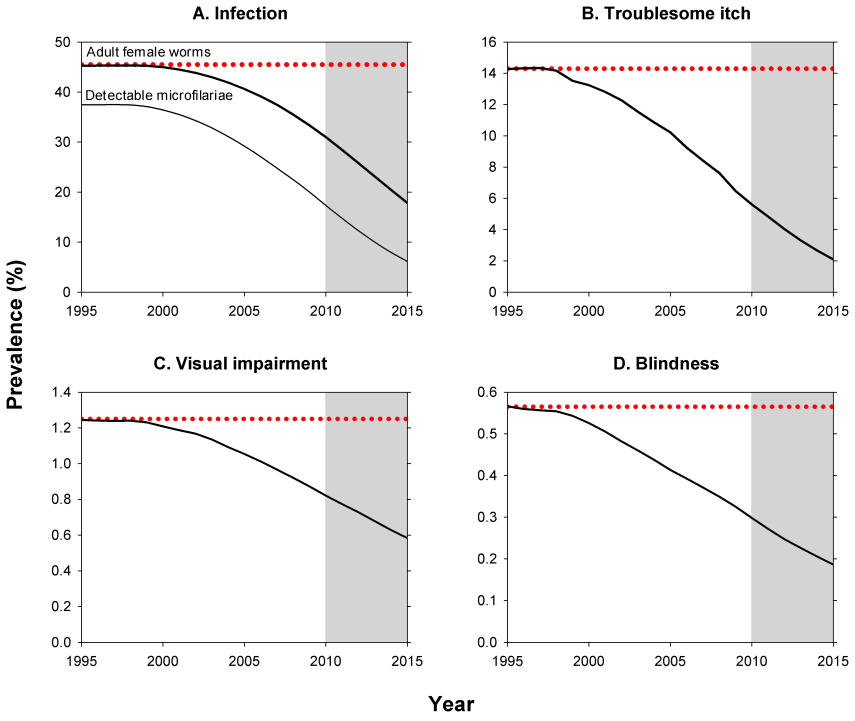

Figure 4.2: Predicted prevalence of onchocercal infection and morbidity in APOC areas from 1995 to 2015. Please note the different scales for the y-axes in the four panels. Shaded areas represent projections for 2011–2015. A) Prevalence of infection is defined as infestation with at least one adult female worm, or alternatively, presence of detectable microfilariae in the skin. B) Prevalence of troublesome itch, caused by onchocerciasis. C) Prevalence of onchocercal visual impairment, defined as corrected visual acuity (i.e. measured with glasses on or through pinhole) of $< 18/60$ and $\geq 3/60$ in the better eye. D) Prevalence of onchocercal blindness, defined as corrected visual acuity (i.e. measured with glasses on or through pinhole) of $< 3/60$ or restriction of visual field to less than 10° in the better eye.

Results

In 1995, the total population size in the APOC target area was 71.5 million (Figure 4.1), with 30 % of the APOC target population living in hyperendemic communities, 31 % in mesoendemic communities, 38 % in hypoendemic communities surrounded by mesoendemic or hyperendemic areas, and 1 % living in nonendemic communities. About 30 % of the APOC population lived in savanna areas and 70 % in forest or forest–savanna mosaic areas (Table 4.1). Before the inception of APOC in 1995, about 32 million people (45 %) in APOC areas were infected with onchocerciasis, with 404,000 people (0.6 %) blind because of onchocerciasis, another 889,000 (1.2 %) suffering from visual impairment, and 10 million people (14 %) suffering from troublesome itch. In the same year, a total of 1.6 million DALYs (22.8 DALYs per 1,000 persons) were lost due to onchocerciasis: 694,000 because of troublesome itch, 684,000 from blindness, and 251,000 due to visual impairment.

Mass treatment effectively started in 1997 (80,000 treatments) and was scaled up over the years, reaching an overall therapeutic coverage of about 73 % in 2010 (75.8 million treatments; Figure 4.1). We estimated that the therapeutic coverage will increase to 78 % by 2015 (92.5 million treatments). By 2010, about 65 % of the population lived in areas subjected to 10–13 rounds of mass treatment, 17 % in areas subjected to 6–9 rounds of mass treatment, 18 % in areas subjected to 3–5 rounds of mass treatment, and less than 1 % in areas subjected to only 1–2 rounds of mass treatment (Table 4.1). Cumulatively, about 500 million treatments with ivermectin were given between 1995 and 2010, with another 430 million expected to follow in the period 2011–2015. Considering the differences between projects in start year and patterns of scaling up of mass treatment, the prevalence of infection for APOC as a whole declined gradually and non-linearly over time, from 45 % in 1995 to 31 % in 2010, and to 18 % in 2015 (Figure 4.2). Similarly, the prevalence of troublesome itch was reduced from 14 % to 6 % to 2 %, and prevalence of visual impairment was reduced from 1.2 % to 0.8 % to 0.6 %. Because of excess mortality among the blind and the fact that ivermectin prevented blindness in individuals who were already visually impaired, the prevalence of blindness declined more rapidly than that of visual

impairment: from 0.6 % to 0.3 % to 0.2 %.

In the counterfactual scenario without mass treatment, in which levels of infection and morbidity were stable, the absolute number of DALYs lost due to onchocerciasis would have increased over the years with population growth. In contrast, in the scenario that considers mass treatment with ivermectin, the absolute number of DALYs lost was predicted to decrease over the years. Due to these divergent trends, the number of DALYs averted by mass treatment with ivermectin was predicted to increase year by year (Figure 4.3). Overall, mass treatment with ivermectin averted 8.2 million DALYs between 1995 and 2010 (3.2 million due to itch, 4.4 million due to blindness, 0.6 million due to visual impairment). Moreover, we expect that APOC will avert another 9.2 million DALYs in the period 2011–2015, adding up to an expected total of 17.4 million averted DALYs by 2015 (Table 4.2). In relative terms, the disease burden of onchocerciasis was reduced from 22.8 DALYs per 1,000 persons in 1995 to 9.6 DALYs per 1,000 persons in 2010, and is expected to be further reduced to 5.0 DALYs per 1,000 persons by 2015.

Univariate sensitivity analyses identified the following parameters as having the most influence on the estimated health impact: the population at risk, pre-control levels of infection, and the associations between infection and itch and eye disease (Figure 4.4). The multivariate sensitivity analysis showed that the estimated cumulative number of DALYs averted could be up to 25 % higher or lower, when we considered the separate sources of uncertainty simultaneously (6.0–9.8 million DALYS cumulatively averted by 2010, and 13.1–21.3 million DALYs cumulatively averted by 2015; Figure 4.4).

Between 1995 and 2010, coordination of mass treatment cost roughly US$257 million (Table 4.2), of which US$175 million was disbursed by APOC and US$82 million by national onchocerciasis task forces (cost of donated drugs and government salaries not included). Assuming that costs will rise proportionally with the number of treatments, mass treatment was expected to cost another US$221 million between 2011 and 2015, adding up to a total cost of US$478 million by 2015.

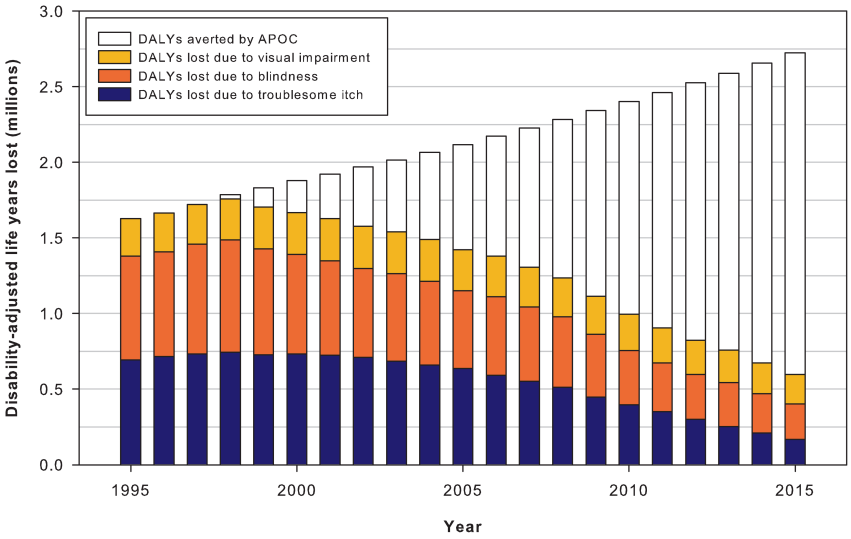

Figure 4.3: Disability-adjusted life years (DALYs) lost due to onchocerciasis from 1995 to 2015. The total height of the bars (colored plus blank) represents the estimated number of DALYs lost in a counterfactual scenario without ivermectin mass treatment (increasing trend due to population growth). The colored part of each bar represents the estimated actual number of DALYs lost (declining trend due to ivermectin mass treatment). The blank part of each bar therefore represents the annual number of DALYs averted by ivermectin mass treatment in the total APOC population.

Discussion

We estimated the health impact and cost of mass treatment with ivermectin for the 20-year period that APOC is scheduled to run as a morbidity control program (1995–2015). Our simulations suggest that mass treatment with ivermectin has markedly reduced the prevalence of infection with *O. volvulus*, troublesome itch, visual impairment, and blindness in APOC areas, averting an estimated 8.2 million DALYs due to onchocerciasis by 2010 at a nominal financial cost of about US$257 million (excluding cost of donated drugs). We expect that APOC will avert another 9.2 million DALYs between 2011 and 2015, at a nominal financial cost of US$221 million.

Our estimate of APOC's health impact only considered eye disease and troublesome itch, and would be even higher if other clinical

manifestations of onchocerciasis would have been taken into account. For instance, disfiguring skin disease also contributes to the disease burden of onchocerciasis and is known to be reduced by ivermectin (Kim 1997; Murdoch et al. 2002; Alonso, Murdoch, and Jofre-Bonet 2009; Ozoh et al. 2011). Further, epilepsy may be associated with onchocerciasis, as suggested by a growing but still uncertain base of evidence (Pion et al. 2009). However, we chose to include only the most important disease manifestations for which data were available for model calibration (i.e. eye disease and troublesome itch). Furthermore, we did not include the effect of ivermectin on diseases that are co-endemic with onchocerciasis, such as soil transmitted helminthiases, ectoparasitic infections, and lymphatic filariasis (Tielsch and Beeche 2004). Other minor factors leading to an underestimation of the health impact are that we only considered the effect of ivermectin on the capacity of adult female worms to release microfilariae and its microfilaricidal effect, whereas ivermectin may additionally have a modest effect on adult worm viability (Awadzi et al. 1999; Gardon et al. 2002). Furthermore, we ignored between-village variation in coverage, which is perhaps most extreme in the phase of scaling up: in some projects, treatment started in a subpopulation with high coverage, while the other part of the population did not yet receive mass treatment (which is more efficient than treating the entire project population at an equivalent average coverage). We may have somewhat overestimated the number of life years lost due to excess mortality from blindness during and after mass treatment, causing a small underestimation in the number of DALYs averted. This is because we appointed a fixed number of life years lost to every new case of blindness, while regular ivermectin treatment is expected to postpone the onset of blindness to a higher age, reducing the number of life years lost due to blindness. Furthermore, we did not consider a possible association between excess mortality and (high) microfilarial load (Little et al. 2004a; Walker et al. 2012).

There are several factors that may (partly) counterweigh the underestimation of the health impact of APOC described above. Therapeutic coverage may have been over-reported by community members responsible for the distribution of ivermectin, either because of incomplete estimates of the community population or to

Table 4.2: Health impact and cost of ivermectin mass treatment, 1995–2015.

Year	Health impact (million DALYs averted)	Costs for coordination of mass treatment (million US$)		
		APOC	NOTF[a]	Total[b]
1995	0.00	0.0	0.0	0.0
1996	0.00	2.4	1.1	3.6
1997	0.00	2.4	1.1	3.6
1998	0.03	9.3	4.4	13.7
1999	0.13	9.3	4.4	13.7
2000	0.21	9.2	4.3	13.5
2001	0.29	9.2	4.3	13.5
2002	0.39	9.1	4.3	13.3
2003	0.47	11.3	5.3	16.7
2004	0.58	12.6	5.1	17.8
2005	0.69	13.5	4.0	17.6
2006	0.79	11.0	6.0	17.0
2007	0.92	13.7	7.7	21.4
2008	1.05	13.7	7.5	21.3
2009	1.23	21.2	10.0	31.1
2010	1.41	26.7	12.5	39.2
2011	1.56			40.2
2012	1.70			42.5
2013	1.83			44.4
2014	1.98			46.3
2015	2.13			47.9
Subtotal 1995–2010	8.20	174.8	82.1	256.9
Total 1995–2015	17.39			478.1

[a] National Onchocerciasis Task Forces. NOTF expenditures for the years 1995–2003 and 2010 were unknown; they were assumed to be equal to 47 % of APOC expenditures, based on known expenditures for the years 2004–2009.

[b] Expenditures for 2011–2015 were estimated based on the expected number of treatments in that period multiplied by the estimated cost per treatment in 2010(US$0.52).

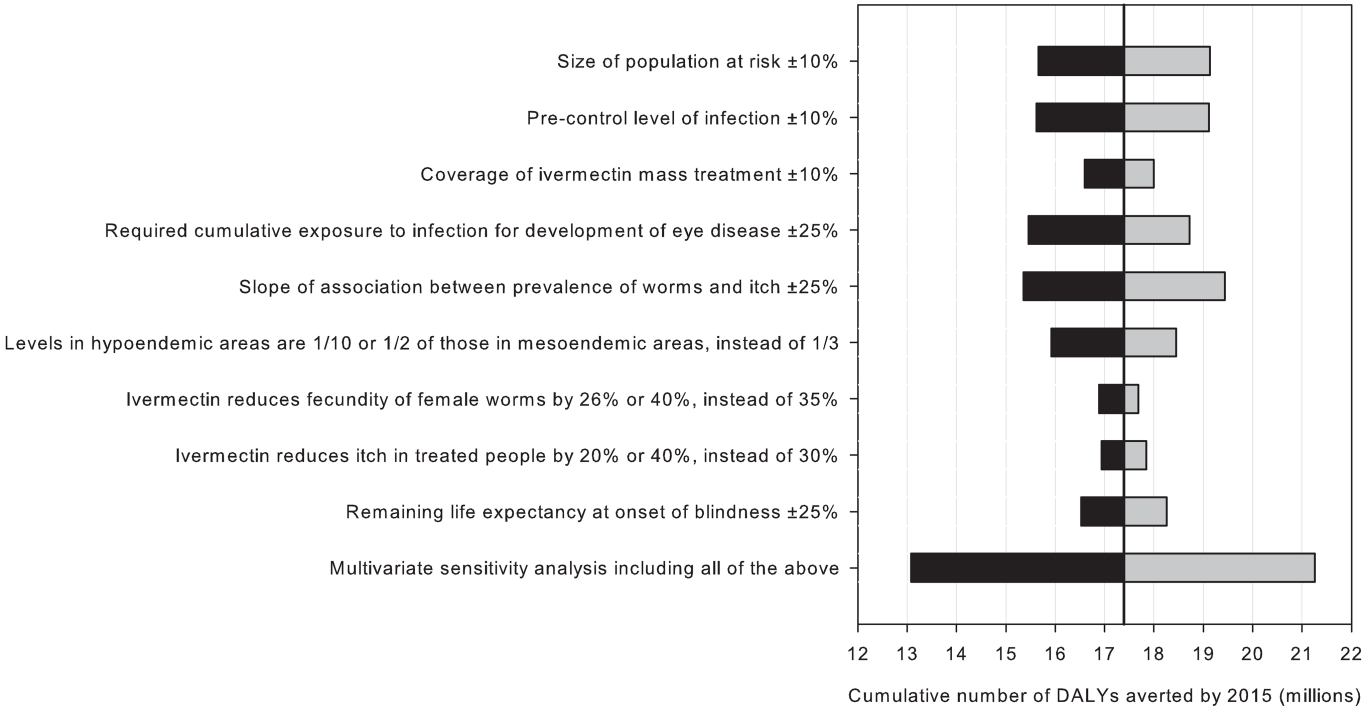

Figure 4.4: Sensitivity analysis for the estimated cumulative number of disability-adjusted life years (DALYs) averted by 2015. The multivariate sensitivity analysis (last item) consisted of 200 repeated analyses, based on 200 sets of random parameter values, which were drawn from triangular distributions with modes equal to parameter values used in the main analysis, and minimum and maximum values equal to parameter values used in the univariate sensitivity analysis (first eight items of this figure). The results of the multivariate sensitivity analysis are expressed as the 2.5^{th} and 97.5^{th} percentiles of results from 200 repeated analyses.

inflate their own performance. Yet, the estimated health impact of APOC by 2015 would decrease by only 0.8 million averted DALYs if we assume that coverage were to be systematically 10 % lower than reported. Also, we ignored any mass treatment prior to the inception of APOC, whereas in reality, ivermectin distribution had already started in a limited number of foci (here morbidity levels had already been reduced somewhat, but not on account of APOC). Taking all above sources of under- and over-estimation into account, we believe that the true health impact of APOC is still slightly higher than our calculations.

The validity of our results, as in any simulation study, depends on the quality of the model and its assumptions. ONCHOSIM was first developed in the early nineties and has earned trust over the years from the large scale control programs. ONCHOSIM has been used to successfully mimic observed epidemiological data from various locations (Plaisier et al. 1991a,b; Alley et al. 1994; Plaisier et al. 1995), and has been used for policy making in the West-African Onchocerciasis Control Programme (Plaisier et al. 1997). Efforts to validate the model continue. We have recently compared ONCHOSIM predictions to longitudinal data from Senegal and Gambia (Diawara et al. 2009; Traore et al. 2012) and found that model-predicted trends in mf prevalence during 14 to 16 years of mass treatment were broadly consistent with the observed trends, although the mf prevalence sometimes seemed to decline slightly faster than predicted (unpublished data). Furthermore, our model predictions for trends in itch were comparable to the reported average trend in APOC sentinel areas (Ozoh et al. 2011); after five to six years of mass treatment at 70–80 % coverage, itch prevalence was reported to decline from 16 % to 7 %, and we predicted a decline from 14 % to 6.5 % for areas with similar pre-control levels of infection and history of mass treatment. Likewise, our model adequately reproduced trends in onchocercal blindness during vector control in West Africa (Appendix B). Although the above suggests that our model predictions are realistic, our estimates remain subject to uncertainty and it would be good to have them confirmed by more field data, especially regarding trends in morbidity during mass treatment.

Even though the model seems to be reliable, we should consider

potentially important sources of uncertainty in our analysis. An often debated factor concerns the effect of ivermectin on adult worms. The univariate sensitivity analysis showed that the assumed treatment effects of ivermectin on the capacity of adult worms to release microfilariae influenced the estimated health impact only marginally. We did not study the effects of assuming no cumulative effects of ivermectin on worm fecundity, whereas it has been suggested that the latter may be the case (Bottomley et al. 2008). However, if we had, ivermectin efficacy parameters would have been calibrated such that the model-predicted trends in mf prevalence and density were still in agreement with observed trends (Alley et al. 1994; Plaisier et al. 1995), and therefore predicted trends in infection levels and morbidity should not have differed much from the current model's predictions. The sensitivity analysis showed that alternative assumptions for the effect of ivermectin on itch (the only reversible symptom under consideration) also influenced the estimated health impact only marginally. The most influential assumptions in our analysis were related to the estimated size of the population at risk, pre-control levels of infection, and the assumed associations between infection and morbidity, which were all based on data. Even though the multivariate sensitivity analysis suggested considerable overall uncertainty in our estimate of the health impact ($\pm 25\,\%$), the magnitude of the predicted impact was always large.

With an estimated 8.2 million DALYs averted in a 15-year period and a predicted doubling in the subsequent 5 years, the predicted health impact of APOC is impressive. According to our calculations, mass treatment against onchocerciasis cost about a nominal US$31 per undiscounted DALY averted between 1995 and 2010. According to World Health Organization guidelines (WHO Commission on Macroeconomics and Health 2001), this is highly cost-effective, as it is below the per capita gross domestic product of most countries covered by APOC (27–1,545 international dollar per capita; Global Health Observatory Data Repository, accessed 2 August 2012). Furthermore, this cost-effectiveness is comparable to or even better than those for several other public health interventions. For example, the life-time costeffectiveness of prophylaxis against mother-to-child transmission of HIV in a resource-limited setting has

been estimated at US$52 per undiscounted DALY (incremental cost-effectiveness ratio of World Health Organization guidelines versus minimal standard of care; Shah et al. 2011). The cost-effectiveness of large-scale, long-term (30-year period) public health interventions targeting other neglected tropical diseases has been estimated at US$4–US$29 per DALY (mass drug administration against lymphatic filariasis), US$38 per DALY (case detection and treatment for leprosy), US$260 per DALY (vector control against Chagas disease), and US$48–US$303 (vector control against lymphatic filariasis; Remme et al. 2006). Mass treatment against onchocerciasis is of even better value (US$27 per DALY) if expected health gains and costs for the period 2011–2015 are included. In view of the anticipated elimination of infection so that mass treatment can be stopped altogether, the cost-effectiveness will be even better than our calculations suggest (Diawara et al. 2009; Tekle et al. 2012; Traore et al. 2012).

The objective of APOC is to establish country-led systems for onchocerciasis control by 2015, which means that countries and their partners will have to carry full financial responsibility by that year. Our results indicate that cost per treatment with ivermectin in APOC areas is affordable (US$0.51 per treatment, excluding cost of donated drugs) and comparable to the costs of existing national mass treatment programs for the elimination of lymphatic filariasis (US$0.06–US$2.23 per treatment; Goldman et al. 2007). Mass treatment with ivermectin, however, also involves costs for society not covered by the program. From published data for two Nigerian communities, we derived that these costs are about US$0.23 per treatment (excluding start-up costs) (Onwujekwe et al. 2002). Based on this estimate, the sum of program and community costs for mass treatment with ivermectin was approximately US$370 million from 1995 to 2010 and will be another US$320 million for 2011–2015. In addition to costs, there are significant benefits for society that countries need to take into account, such as prevented productivity losses resulting from blindness and itch. Blindness in rural Africa has previously been assumed to result in an annual productivity loss of US$150 per case (Benton 1998). Likewise, the productivity loss due to itch among coffee plantation workers in an Ethiopian site has been

estimated at around US$5.32 per month per case (Workneh, Fletcher, and Olwit 1993; Kim 1997). Combined with our predictions of health impact, these figures suggest that by 2015, APOC will have averted a staggering US$2.2 billion due to productivity losses from blindness (US$517 million) and itch (US$1.7 billion, assuming productivity losses in 25 % of people with itch). In other words, beneficiary countries should expect economic benefit from mass treatment that outweighs any costs.

Clearly, all of the above calculations apply only under the condition that countries do not themselves pay for the drug ivermectin. The amount of ivermectin donated up to 2010 represents a value of US$2.1 billion, assuming 2.8 tablets per treatment and a commercial price per tablet of US$1.50 plus US$0.005 shipping costs (personal communication with Dr. A.D. Hopkins, director of the Mectizan Donation Program). This amount is eight times the program costs for coordinating mass treatment. Likewise, for the period 2011–2015, the value of donated ivermectin will be an additional US$1.8 billion. Therefore, mass treatment with ivermectin can be sustained only with donation of ivermectin, which Merck has pledged to continue for as long as necessary.

We expect that levels of infection in the APOC target area will have fallen drastically by 2015 (overall prevalence of adult female worms 18 %). The implication is that by that time, transmission of infection may be almost interrupted in areas with favorable conditions for elimination, such as high coverage of mass treatment, sufficient treatment rounds, and/or low to medium pre-control levels of infection (Winnen et al. 2002). Until recently, elimination of onchocerciasis from Africa was thought to be impossible by means of mass treatment alone, considering the large size of the transmission zones, mobility of the vectors and human populations, and poor compliance with mass treatment (Dadzie, Neira, and Hopkins 2003). Following reports of elimination of onchocerciasis from foci in Mali and Senegal by mass treatment alone (Diawara et al. 2009; Traore et al. 2012), however, interest has renewed in elimination of onchocerciasis from Africa (Mackenzie et al. 2012). Following this, WHO has recently been advised to extend APOC mandate by ten years to 2025 with the new aim of eliminating infection with O.

volvulus, where possible. With this new motivation, we may indeed expect focal elimination of infection, resulting in even more health gains from mass treatment with ivermectin in the future and the possibility of being able to end mass treatment altogether.

According to our simulations, APOC has had a remarkable impact on population health in Africa between 1995 and 2010. This health impact is expected to double during the subsequent five years. Further, APOC is a highly cost-effective public health programs, and given the anticipated elimination of onchocerciasis from APOC areas, we expect even more health gains and a more profitable cost-effectiveness of mass treatment with ivermectin in the near future. Our study fully supports the advice to continue APOC activities for another ten years.

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Chapter 5

African Programme for Onchocerciasis Control 1995–2015: updated estimates of the health impact based on new disability weights

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Submitted for publication

Abstract

Previously, we provided in this journal an estimate of the health impact of ivermectin mass treatment coordinated by the African Programme for Onchocerciasis Control (APOC). Here, we re-estimate the health impact of APOC in terms of disability adjusted life years (DALYs), based on previously published, model-predicted estimates of number of cases with visual impairment, blindness, and troublesome itch, using updated disability weights from the Global Burden of Disease 2010 study. These updated disability weights better reflect our ideas and beliefs as a society of what constitutes health. According to our updated estimates, between 1995 and 2010 APOC has averted 8.9 million DALYs (5.1 million due to itch, 70 thousand due to visual impairment, and 3.7 million due to blindness), and it will avert another 10.1 million DALYs between 2011 and 2015. The updated estimates of the health impact of APOC are only slightly higher than previous estimates. However, due to changes in disability weights, onchocercal skin disease is now the most important contributor to the burden of onchocerciasis, instead of eye disease.

Since 1995, the African Programme for Onchocerciasis Control (APOC) has coordinated mass treatment with ivermectin in 16 sub-Saharan countries with the aim to control morbidity due to infection with Onchocerca volvulus, a filarial nematode. Recently, we predicted trends in prevalence of infection, visual impairment, blindness, and troublesome itch due to onchocerciasis for the period 1995–2015, based on extensive data on pre-control infection levels, population coverage of ivermectin mass treatment, and the association between infection and morbidity (Coffeng et al. 2013b). We also estimated the associated health impact, expressed in disability-adjusted life years (DALYs). However, the estimated health impact was based on disability weights from the 2004 update of the Global Burden of Disease (GBD) study (WHO 2004), which have been criticized for being based solely on the opinions of health professionals (Mont 2007; King and Bertino 2008). The recently published GBD 2010 Study addressed this criticism by providing updated disability weights based on household surveys in Bangladesh, Indonesia, Peru, and Tanzania, an open internet survey, and a telephone survey in the United States of America (Salomon et al. 2012). As a result of this population-based approach, the disability weights for visual impairment, blindness, and troublesome itch have changed considerably, and should better reflect our ideas and beliefs as a society of what constitutes health. For future reference, we provide an updated estimate of the health impact of APOC activities, based on previously predicted trends in averted number of cases with infection and morbidity, but using updated disability weights for visual impairment, blindness, and troublesome itch.

Identical to previously used methods (Coffeng et al. 2013b), we calculated the health impact of APOC for each year between 1995 and 2015, expressed in DALYs averted. The DALY metric is the sum of years of life lost (YLL) due to premature mortality (from blindness) and years lived in disability (YLD), weighted by a disability weight representing the loss of quality of life (Salomon et al. 2012). DALYs averted were calculated as the difference between two scenarios: a factual scenario in which APOC activities have taken place as documented, and a counterfactual scenario in which APOC

activities have not taken place at all, effectively translating to:

$$\begin{aligned} \mathrm{DALY}_{\mathrm{averted}} &= \Delta\mathrm{YLL}_{\mathrm{blindness}} + \Delta\mathrm{YLD}_{\mathrm{blindness}} + \\ &\quad \Delta\mathrm{YLD}_{\mathrm{visual\ impairment}} + \Delta\mathrm{YLD}_{\mathrm{itch}} \end{aligned}$$

Here, $\Delta\mathrm{YLL}_{\mathrm{blindness}}$ is the averted number YLL related to premature mortality from blindness (as previously estimated; Coffeng et al. 2013b), and $\Delta\mathrm{YLD}_{\mathrm{x}}$ is the averted number of YLD due to symptom x. Averted YLD were calculated as $\Delta\mathrm{YLD}_{\mathrm{x}} = \Delta\mathrm{N}_{\mathrm{x}} \times \mathrm{dw}_{\mathrm{x}}$, where $\Delta\mathrm{N}_{\mathrm{x}}$ is the averted number of person-years of symptom x (i.e. difference between the factual and counterfactual scenarios, as previously estimated Coffeng et al. 2013b), and dw_{x} is the associated updated disability weight, derived from the GBD 2010 study (Salomon et al. 2012).

Compared to previous disability weights (WHO 2004), updated weights were considerably lower for visual impairment (0.033, previously 0.282) and blindness (0.195, previously 0.594), reflecting that the loss in quality of life because of these manifestations is considerably lower than previously assumed. On the contrary, the disability weight for troublesome itch has increased (0.108, previously 0.068). The disability weight for visual impairment represents "moderate visual impairment" in the GBD 2010 study. The disability weight for troublesome itch was derived from a generic class of disability weights for "disfigurement with itch or pain". This class consists of three severity levels, characterized as "causing some worry and discomfort" (disability weight 0.029), "a person having trouble concentrating and sleeping" (disability weight 0.187), and "causing a person to avoid social contact, feel worried, sleep poorly, and think about suicide" (disability weight 0.562). Based on previously published data (Murdoch et al. 2002), we assumed that onchocercal itch causes insomnia in about half of the cases, and therefore calculated YLD due to itch using the mean of the disability weights for the first two severity levels (0.108).

Figure 5.1 illustrates trends in DALYs lost due to troublesome itch, visual impairment, and blindness, and DALYs averted by APOC. Table 5.1 gives more detailed information on the number of prevalent cases (according to the factual scenario) and DALYs lost and averted per year. For onchocercal visual impairment and blindness,

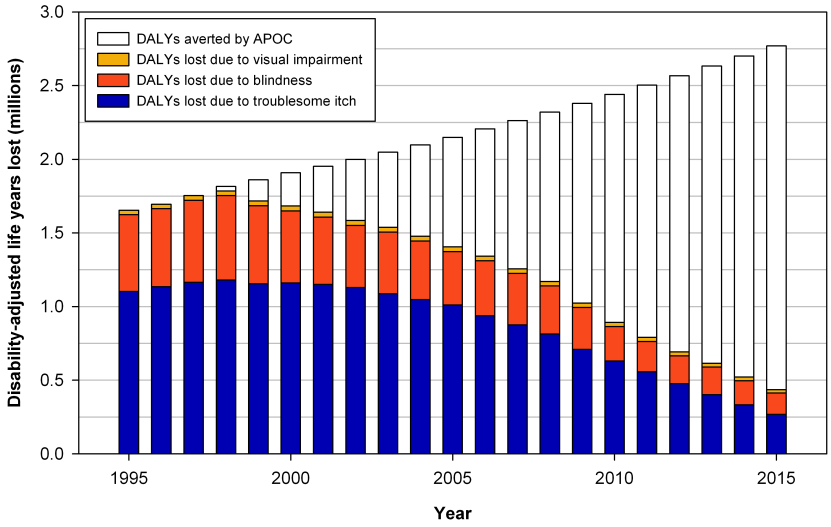

Figure 5.1: Disability-adjusted life years (DALYs) lost due to onchocerciasis from 1995 to 2015. The total height of the bars (colored plus blank) represents the estimated number of DALYs lost in a counterfactual scenario without ivermectin mass treatment (increasing trend due to population growth). The colored part of each bar represents the estimated actual number of DALYs lost (declining trend due to ivermectin mass treatment). The blank part of each bar therefore represents the annual number of DALYs averted by ivermectin mass treatment in the total APOC population.

the updated estimates of the averted burden turned out lower than the previous estimates. In contrast, for troublesome itch, the updated estimate of the averted turned out higher than the previous estimate. For visual impairment and troublesome itch, the difference between previous and updated estimates was proportional to the change in values of the associated disability weights. For blindness however, this difference was not proportional, as the burden of blindness also included years of life lost due to premature mortality (which is exactly the same for previous and updated estimates).

Overall, we estimated that APOC has cumulatively averted 8.9 million DALYs due to onchocerciasis through 2010, and will avert another 10.1 million DALYs between 2011 and 2015, adding up to a total of 19.0 million DALYs averted through 2015. These updated

estimates do not differ much from previous estimates (8.2 million DALYs averted through 2010, and another 9.2 million between 2011 and 2025). In relative terms, the burden of onchocerciasis in APOC areas has decreased from 23.1 DALYs per 1,000 persons in 1995 to 8.6 DALYs per 1,000 persons in 2010, and is expected to further decrease to 3.7 DALYs per 1,000 persons in 2015.

The updated disability weights provided by the GBD 2010 study are based on population surveys rather than expert opinion. Therefore, they should better reflect our ideas and beliefs as a society of what constitutes health than previous disability weights (Salomon et al. 2012). However, there is still some debate about whether the updated disability weight are too high or too low, particularly those for visual impairment and blindness (Salomon, Vos, and Murray 2013; Taylor et al. 2013). Systematic reviews and meta-analyses are needed to clarify this matter. Nevertheless, according to our updated estimates, skin disease is now the most important contributor to the burden of onchocerciasis, rather than eye disease. Moreover, the true disease burden of onchocercal skin disease (and the burden averted by APOC) is still larger than we estimate here, as our updated estimates do not include disfiguring skin disease. This additional burden is probably considerable, given the relatively high values of the updated disability weights for disfiguring skin disease and the high pre-control prevalence of disfiguring skin disease in areas endemic for onchocerciasis (Murdoch et al. 2002). This underlines the importance of onchocercal skin disease, especially in forest areas where vision loss is relatively rare (Murdoch 2010).

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Table 5.1: Population at risk, number of cases, and disability-adjusted life years lost and averted due to onchocerciasis in APOC regions.

Year	Population size and number of cases of infection and disease in APOC areas (thousands)					Disability-adjusted life years lost (thousands)				Disability-adjusted life years averted (thousands)			
	Population (at risk of infection)	Infected[a]	Troublesome itch	Visual impairment	Blindness	Troublesome itch	Visual impairment	Blindness	Total	Troublesome itch	Visual impairment	Blindness	Total
1995	71,474	32,330	10,202	889	404	1,102	29	523	1,654	0	0	0	0
1996	73,310	33,209	10,499	910	410	1,134	30	530	1,694	0	0	0	0
1997	75,195	34,073	10,780	931	418	1,164	31	558	1,753	0	0	0	0
1998	77,132	34,951	10,925	957	427	1,180	32	573	1,785	9	0	21	30
1999	79,122	35,816	10,692	974	430	1,155	32	530	1,717	65	0	79	144
2000	81,165	36,522	10,749	981	427	1,161	32	489	1,683	90	1	135	226
2001	83,144	36,998	10,653	987	420	1,151	33	457	1,640	131	1	180	312
2002	85,172	37,338	10,456	995	410	1,129	33	421	1,583	183	2	231	416
2003	87,249	37,502	10,073	990	402	1,088	33	417	1,538	256	3	251	510
2004	89,377	37,458	9,705	977	391	1,048	32	397	1,477	329	4	288	621
2005	91,558	37,196	9,357	965	379	1,011	32	363	1,405	400	6	338	744
2006	93,928	36,779	8,684	951	369	938	31	373	1,342	509	7	349	864
2007	96,360	36,093	8,111	931	358	876	31	349	1,256	608	9	390	1,007
2008	98,857	35,085	7,539	910	345	814	30	327	1,171	708	10	431	1,149
2009	101,419	33,811	6,564	885	330	709	29	285	1,024	852	12	492	1,356
2010	104,050	32,246	5,836	854	310	630	28	234	892	971	14	563	1,549
2011	106,750	30,355	5,157	825	290	557	27	206	790	1086	16	611	1,713
2012	109,521	28,244	4,417	797	271	477	26	189	692	1208	18	648	1,875
2013	112,366	25,979	3,724	762	254	402	25	188	615	1327	21	670	2,018
2014	115,287	23,591	3,074	724	237	332	24	165	521	1442	23	715	2,179
2015	118,285	21,115	2,478	690	220	268	23	145	435	1552	25	757	2,334
Subtotal 1995–2010						16,289	498	6,827	23,614	5,110	70	3,748	8,929
Total 1995–2015						18,325	623	7,719	26,667	11,724	174	7,149	19,048

[a] Infection defined as presence of at least one adult female worm.

Chapter 6

African Programme for Onchocerciasis Control: impact of annual ivermectin mass treatment on off-target infectious diseases

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Abstract

Since its initiation in 1995, the African Program for Onchocerciasis Control (APOC) has had a substantial impact on the prevalence and burden of onchocerciasis through annual ivermectin mass treatment. Ivermectin is a broad-spectrum anti-parasitic agent that also has an impact on other co-endemic parasitic infections. In this study, we roughly assessed the additional impact of APOC activities on the burden of the most important off-target infections: soil-transmitted helminthiases (STH; ascariasis, trichuriasis, hookworm, and strongyloidiasis), lymphatic filariasis (LF), and scabies. Based on a literature review, we formulated assumptions about the impact of ivermectin treatment on the disease burden of these off-target infections. Using data on the number of ivermectin treatments in APOC regions and the latest estimates of the burden of disease, we then calculated the impact of APOC activities on off-target infections in terms of disability-adjusted life years (DALYs) averted. We conservatively estimated that between 1995 and 2010, annual ivermectin mass treatment has cumulatively averted about 500 thousand DALYs from co-endemic STH infections, LF, and scabies. This impact comprised an additional 5.5 % relative to the total burden averted from onchocerciasis (9 million DALYs), and indicates that the overall cost-effectiveness of APOC is even higher than previously reported.

Introduction

The African Program for Onchocerciasis Control (APOC) is an international program aimed at elimination of human onchocerciasis (river blindness) as a disease of public health importance in sub-Saharan Africa (SSA), using mass drug treatment (Amazigo 2008). Since its launch in 1995, APOC has scaled up geographically, averting 9 million disability-adjusted life years (DALYs) through 2010, and eventually aiming to treat over 90 million people annually in 16 African countries by 2015, protecting a population at risk of onchocerciasis of 118 million (see also Chapter 4 and Chapter 5; Coffeng et al. 2013b). The drug used for mass treatment of onchocerciasis, ivermectin, is distributed and administered in a single dose of 150 to 200 $\mu g\,kg^{-1}$ of body weight annually. Pregnant (or lactating) women and children under five are excluded from treatment with ivermectin (Amazigo 2008).

Ivermectin is known to be effective against various infectious diseases other than onchocerciasis, the most important being soil-transmitted helminth (STH) infections, lymphatic filariasis (LF), and epidermal parasitic skin diseases (EPSDs) such as scabies (Campbell 1991; Dourmishev, Dourmishev, and Schwartz 2005; Bethony et al. 2006; Ottesen et al. 2008; Feldmeier and Heukelbach 2009; Hotez and Kamath 2009; Brooker, Hotez, and Bundy 2010). In APOC countries, the prevalence of STH infections in school-age children ranges between 20 % and 50 % (London School of Hygiene and Tropical Medicine 2009). LF is endemic in all APOC countries (London School of Hygiene and Tropical Medicine 2009; Brooker, Hotez, and Bundy 2010) with an estimated prevalence of 6 % to 9 % [6]. Despite the lack of comprehensive epidemiological data, it is known that EPSDs are prevalent across SSA and that the associated morbidity is significant in regions of high poverty (Feldmeier and Heukelbach 2009; Murray et al. 2012). Together, these infections are responsible for a considerable burden of disease (Murray et al. 2012). Therefore, annual mass treatment with ivermectin is expected to have an additional health impact by averting part of the burden related to these off-target infections (Taticheff et al. 1994; Tielsch and Beeche 2004; Anosike et al. 2007; Ottesen et al. 2008; Gutman et al. 2010). Up till now, this additional health impact has not been

quantified and its importance remains unknown.

In this study, we quantified the health impact of APOC activities through 2010 on the burden of STH (ascariasis, trichuriasis, hookworm, and strongyloidiasis), LF, and scabies. We reviewed the literature to retrieve field studies examining the effect of ivermectin treatment on off-target infections and formulated assumptions about the impact of ivermectin mass treatment on the associated burden of disease. Next, we retrieved estimates of the disease burden of candidate off-target diseases from the Global Burden of Disease (GBD) 2010 Study (Murray et al. 2012). By combining this information with data on the number of ivermectin treatments given through 2010 (recorded by APOC), we roughly estimated the number of DALYs due to off-target infections averted by APOC.

Methods

Assumptions about effect of ivermectin on burden of off-target infections

We first performed a systematic PubMed search to determine ivermectin efficacy against off-target infection, defined as the ability to provide a clinically measurable and preferably beneficial effect. We used the key term "ivermectin" in combination with any of the following: "efficacy", "mass treatment", "morbidity control", "soil-transmitted helminth infections", or "skin disease". Searches were made without time limitations. If available, meta-analysis studies evaluating the efficacy of ivermectin against a specific disease were used. If meta-analysis studies were not available, clinical studies reporting the efficacy of treatment were selected if: (1) the treatment regime concerned a single dose of about 150 to 200 $\mu g\,kg^{-1}$ of body weight, and (2) the efficacy was evaluated up to one month for STH infections and up to a year for filarial infections and EPSDs. We considered a month to be the threshold duration of the immediate effect of ivermectin on STH infections. For LF and EPSDs, longer periods were considered due to a lack of studies evaluating the efficacy of ivermectin as soon as one month after administration. Only studies reporting their results in terms of the following criteria were considered: (1) percent of patients cured and/or percent egg reduction

for STH infections, (2) percent microfilaria (mf) reduction (microfilaricidal efficacy) and/or the percent reduction of fecund females (embryostatic efficacy) in LF, and (3) percent of patients cured for EPSDs. For some EPSDs, clinical studies describing single cases were considered due to the rareness of their incidence. If repeated dose were given, it was noted.

Based on the results of the literature review, we formulated assumptions about the effect of ivermectin treatment on the burden of off-target infections, in terms of reduction in DALYs lost (Box 1). Assumptions were formulated while considering the following factors: the efficacy of ivermectin, the clinical manifestations of each disease, the short and long term effects of mass treatment on morbidity, and the patterns of post-treatment re-infection. The effect of ivermectin was expressed as parameter (range 0–1), which represents the average annual effectiveness of ivermectin against infection x over a period of six years. The six-year period was based on APOC data on population coverage of ivermectin mass treatment, which suggest that most of the population in APOC areas has been subject to at least six rounds of mass treatment between 1995 and 2010 (Coffeng et al. 2013b). For infections such as STH and scabies, in which morbidity is highly correlated with intensity of infection (parasite load), and transmission is influenced to a small extent, we assumed that treatment rounds have a similar impact on the burden from one year to the next. For LF, repeated mass treatment rounds are expected to have an increasingly higher impact on the disease burden, through the effects of mass treatment on transmission and prevention of further exposure to infection that would lead to chronic disability (e.g. lymphedema). We assumed that for LF, parameter β_x represents the average health impact in areas subject to both shorter and longer periods of ivermectin mass treatment.

Data sources for estimates of disease burden

From the GBD 2010 study (Murray et al. 2012), we derived country-specific estimates of the burden per capita (DALYs lost per 100,000 persons) for ascariasis, trichuriasis, hookworm, LF, and scabies in 1995, 2000, 2005, and 2010 (extracted from the online GBD data

visualization tool[1]). For the years in between, we assumed that the disease burden of these off-target infections followed a trend consistent with linear interpolation of the available estimates. For some countries covered by APOC, the GBD 2010 study reports a decline in the burden of off-target diseases between 1995 and 2010. In the current study, we assume that this decline is not due to APOC activities, at worst leading to an underestimation of the health impact of ivermectin mass treatment on off-target diseases.

Though the group of EPSDs consists of several infections such as scabies, tungiasis (sand fleas), pediculosis (lice), and several other infections (Feldmeier and Heukelbach 2009), for the purpose of this study, we only considered scabies, as burden estimates have been made only for this particular infection so far. Further, the GBD 2010 study does not provide estimates for the burden of strongyloidiasis, an STH, even though its prevalence in SSA is probably considerable. We assumed that the burden due to strongyloidiasis amounts to 1/5 of the total burden caused by the three major STH infections (ascariasis, trichuriasis, and hookworm). This assumption was based on the estimate that the prevalence of the three major STH infections in SSA ranges between 20 % to 50 % (London School of Hygiene and Tropical Medicine 2009), and a large cross-sectional study in rural Ghana which reported a prevalence of strongyloidiasis of 11.6 % (Yelifari et al. 2005). These figures suggest that the prevalence and presumably the burden of strongyloidiasis may be up to five times lower than the prevalence and burden of the other three more common STH infections.

Calculation of disease burden averted

We calculated the disease burden averted, A_{iyx} (in DALYs), for each selected off-target infection x and summed it over the sixteen countries in which APOC has been active between 1995 and 2010 using the following formula, where i represents a specific APOC

[1] http://www.healthmetricsandevaluation.org/gbd/visualizations/country, accessed 30 March 2013

country and y represents the year of mass treatment:

$$A_x = \sum_{i=1}^{16} \sum_{y=1995}^{2010} A_{iyx} = \sum_{i=1}^{16} \sum_{y=1995}^{2010} \beta_x T_{iy} h_{ix} \frac{1 - p_{M_c x} - p_{M_w x}}{1 - p_c - p_w} M_{ixy}$$

In this formula, the annual burden per capita M_{iyx} due to infection x (i.e. burden per capita as reported by the GBD 2010 study) was adjusted to represent the burden per capita in population in APOC areas eligible for mass treatment with ivermectin. This included adjusting for over- or underrepresentation of the disease burden in children under five and pregnant or lactating women (based on the fraction of the disease burden in children under five ($p_{M_c x}$) and pregnant or lactating women ($p_{M_w x}$), and the proportion of children under five (p_c) and pregnant or lactating women (p_w) in the population), and adjusting for clustering of disease burden in APOC regions compared to other country regions (h_{ix}). The adjusted burden per capita was then multiplied by the number of treated individuals T_{iy} for any given year y (extracted from APOC records), yielding the potential disease burden in treated people. Assumptions about the values of aforementioned parameters can be found in Table 6.1, along with the associated literature references. The potential disease burden in treated people was multiplied with the infection-specific ivermectin efficacy β_x, yielding the estimated averted disease burden related to infection x in country i for year y. Results were then summed over years and countries, resulting in a total estimated number of DALYs averted (A_x), related to infection x.

Sensitity analysis

A univariate sensitivity analysis was performed to assess how the main result (number of DALYs averted related to off-target infections) changed when parameter was increased or decreased by 20 %. The value of 20 % was chosen because larger increases or decreases of the effectiveness of ivermectin against off-target infections are highly unlikely to occur in field settings. Likewise, the assigned value of was varied by ±20 %. In addition, prevalence and burden of STH infections or EPSDs were assumed to either be overrepresented in APOC regions for all or none of the countries covered by APOC.

The impact of the assumption regarding burden due to strongyloidiasis (1/5 of the total burden due to other STH infections) was examined by halving or doubling the chosen proportion. Finally, we also performed a multivariate sensitivity analysis by simultaneously increasing or decreasing all assumed parameters by 20 % as an extreme scenario.

Box 6.1: Reasoning and assumptions regarding the effectiveness of an average round of mass treatment (parameter β_x).

Ascariasis A single dose of ivermectin is highly efficacious against *Ascaris lumbricoides*, reducing fecal egg counts by 94–100 % (Freedman et al. 1989; Belizario et al. 2003), and clearing infection in 78–100 % (Richard-Lenoble et al. 1988; Freedman et al. 1989; Naquira et al. 1989; Belizario et al. 2003; Wen et al. 2008). The clinical manifestations of ascariasis include: malnutrition, intestinal obstruction, growth and cognitive delays (Hotez et al. 2007). They are associated with high intensity of infection (worm burden) (de Silva, Guyatt, and Bundy 1997). The immediate post-treatment health benefits include: weight/height gain, increased fitness and physical activity (Bethony et al. 2006; Albonico et al. 2008). The long-term health benefits of treatment include: prevention of intestinal obstruction, increased school attendance, learning abilities, and cognitive testing (Bethony et al. 2006; Anosike et al. 2007; Albonico et al. 2008; Moncayo et al. 2008). Field studies show that post-treatment reinfection does not bring the worm burden or prevalence back to pre-treatment levels in treated communities (Elkins, Haswell-Elkins, and Anderson 1988; Whitworth et al. 1991b; Gutman et al. 2010). Based on this information, we assume that an average round of mass treatment with ivermectin reduces the burden of ascariasis by 50 % ($\beta_x = 0.5$).

Trichuriasis A single dose of ivermectin has medium to high efficacy against *Trichuris trichiura*, reducing fecal egg counts by 86–93 % (Freedman et al. 1989; Naquira et al. 1989), and clearing infection in 35–67 % (Freedman et al. 1989; Naquira et al. 1989; Belizario et al. 2003; Wen et al. 2008). The clinical manifestations of trichuriasis include: inflammatory bowel disease, growth and cognitive delays (Hotez et al. 2007), which are associated with high intensity of infection (worm burden). The immediate post-treatment health benefits include: weight/height gain, increased fitness and physical activity (Bethony et al. 2006; Albonico et al. 2008). The long-term health benefits of treatment include: prevention of inflammatory bowel disease, increased school attendance, learning abilities, and cognitive testing (Bethony et al. 2006; Anosike et al. 2007; Albonico et al. 2008; Moncayo et al. 2008). Field studies show that post-treatment reinfection does not bring the worm burden or prevalence back to pre-treatment lev-

els in treated communities with high initial prevalence (Whitworth et al. 1991b; Moncayo et al. 2008; Gutman et al. 2010)[13,39,40]. Based on this information, we assume that an average round of mass treatment with ivermectin reduces the burden of trichuriasis by 50 % ($\beta_x = 0.5$).

Hookworm infections A single dose of ivermectin has low efficacy against *Ancylostoma duodenale* and *Necator americanus*, reducing fecal egg counts by 52–80 % (Freedman et al. 1989; Wen et al. 2008), and clearing infection in 12–33 % (Freedman et al. 1989; Xia et al. 1992; Wen et al. 2008). The clinical manifestations of hookworm include: iron-deficiency anemia, malnutrition, growth and cognitive delays, and poor pregnancy outcomes (Hotez et al. 2007). They are associated with high intensity of infection (worm burden). A round of mass treatment has a small impact on the worm burden due to the low efficacy of the drug (Whitworth et al. 1991b). The immediate post-treatment health benefits include: weight/height gain, increased fitness (Bethony et al. 2006; Albonico et al. 2008). The long-term health benefits of treatment include: prevention of anemia, malnutrition, growth and cognitive delays. Field studies show that post-treatment reinfection brings the prevalence back to pre-treatment values (Moncayo et al. 2008; Gutman et al. 2010). Based on this information, we assume that an average round of mass treatment with ivermectin reduces the burden of hookworm infections by 20 % ($\beta_x = 0.2$).

Strongyloidiasis A single dose of ivermectin is highly efficacious against *Strongyloides stercoralis*, reducing fecal egg counts by 94–100 % (Freedman et al. 1989; Naquira et al. 1989), and clearing infection in 83–100 % (Naquira et al. 1989; Shikiya et al. 1991, 1992; Datry et al. 1994; Taticheff et al. 1994). Ivermectin is considered to be the drug of choice (Datry et al. 1994; Marti et al. 1996; Nontasut et al. 2005) for treating strongyloidiasis. A round of mass treatment rapidly lowers the worm burden the population (Naquira et al. 1989; Whitworth et al. 1991b; Shikiya et al. 1992; Marti et al. 1996). The clinical manifestations of strongyloidiasis include: abdominal pain and discomfort, diarrhea, weight loss, pruritus, and the potentially deadly dissemination (hyperinfection) (Olsen 2007). The immediate post-treatment health benefits include: prevention of abdominal pain and discomfort, prevention of diarrhea, weight gain (Olsen 2007; Santiago and Leitão 2009). The long-term health benefits of treatment include: prevention of potentially fatal dissemination of infection (Santiago and Leitão 2009). Although strongyloides can persist in an untreated individual for years due to autoinfection (Stern and Joshpe 1971), once eradicated during treatment, an individual can only be re-infected from the environment. Since no follow up studies were found in the literature for *S. stercoralis* reinfection, we assume that the environmental reinfection rate would be similar to that of other STH infections. Based on this information, we assume that an average round of mass treatment with ivermectin reduces

the morbidity due to strongyloidiasis by 50 % ($\beta_x = 0.5$).

Lymphatic filariasis (LF) A single dose of ivermectin has high microfilaricidal (100 %) and intermediate embryostatic (35 %) efficacy against LF (Plaisier et al. 1999). Microfilariae start to reappear at three months post treatment and reaches approximately 11 % of pre-treatment values at twelve months (Dunyo, Nkrumah, and Simonsen 2000). The clinical manifestations of LF include: adenolymphangitis, lymphedema, and hydrocele. Clearing the microfilaria has little clinical significance initially, but through repeated treatments it prevents progression of clinical manifestations (Taylor, Hoerauf, and Bockarie 2010). Annual ivermectin mass treatment does not interrupt the transmission of LF (Richards et al. 2005). Based on this information, we assume that an average round of mass treatment with ivermectin reduces the morbidity due to LF by 10 % ($\beta_x = 0.1$).

Epidermal parasitic skin diseases (EPSDs) A single dose of ivermectin is highly efficacious against EPSDs (Dourmishev, Dourmishev, and Schwartz 2005), causing an immediate lowering of the intensity of infestation. One dose of ivermectin suppresses scabies infection for up to three months (Kar, Mania, and Patnaik 1994) and even clears infestation in 70–100 % (Meinking et al. 1995; Usha and Gopalakrishnan Nair 2000; Sule and Thacher 2007)[56,57,58]. A round of mass treatment lowers the intensity of infestation rapidly (Heukelbach et al. 2004; Abedin et al. 2007). The clinical manifestations of EPSDs include: pruritus (itching), and secondary streptococcal infections (Feldmeier and Heukelbach 2009). The immediate post-treatment health benefits include: prevention of secondary infections, decreased physical and mental discomfort of severe pruritus, increased libido (Hengge et al. 2006; Anosike et al. 2007; Badiaga et al. 2008). The long-term health benefits of treatment include: prevention of streptococcal pyoderma which in turn predisposes to rheumatic fever, acute glomerulonephritis and their respective long-term sequelae: rheumatic heart disease and chronic renal insufficiency (Lawrence et al. 2005; Cestari, Pessato, and Ramos-e-Silva 2007; Feldmeier 2009; Feldmeier and Heukelbach 2009; Gilmore 2011). Based on this information, we assume that an average round of mass treatment with ivermectin reduces the morbidity due to EPSDs by 50 % ($\beta_x = 0.5$).

Table 6.1: Description of parameters and their values.

Parameter	Description	Assumption or reference
M_{ix}	Estimated burden of disease per capita for each country i and disease x between 1995–2010	Global Burden of Disease 2010 study (Murray et al. 2012)
T_{iy}	Number of people treated	Coverage data from APOC records that were also used in a recent evaluation of the health impact and cost of APOC activities (Coffeng et al. 2013b).
h_{ix}	Heterogeneity index	The spread of STH infections in APOC countries was assessed by visually comparing REMO maps (Noma et al. 2002) with maps published by the Global Atlas of Helminth Infections (London School of Hygiene and Tropical Medicine 2009). $h = 1.0$, when STH infections are highly prevalent across the whole country and $h = 1.5$ when certain areas of high prevalence of STH infections overlap APOC regions. For LF, $h = 1.0$ for all countries. For all other infections, $h = 1.5$ for CAR, Chad and Nigeria (as APOC covers about half of the aforementioned countries, the hypothetical maximum value of h would be 2.0 for those countries). For all other countries, we assumed $h = 1.0$.
$p_c + p_w$	Proportion of children below five years of age and pregnant women in the population	Assumed to be 0.2, based on data from U.S. Census Bureau International Database.
β_x	The average annual reduction in DALYs due to infection x over six annual rounds of treatment	See Box 1

Table 6.2: Burden of off-target infections averted by annual ivermectin mass treatment with ivermectin in Africa. Figures represent the cumulative burden averted between 1995 and 2010 in areas covered by the African Programme for Onchocerciasis Control.

Country	Burden averted by ivermectin mass treatment (DALYs x 1,000)[a]							
	Ascarisis	Trichuriasis	Hookworm	Strongy-loidiasis	Lymphatic filariasis	Scabies	Total	%
Angola	0.2	0.1	0.2	0.2	0.1	0.2	0.9	0.2%
Burundi	0.4	0.1	1.3	0.9	0.7	1.2	4.6	1%
Cameroon	24.0	6.2	5.7	8.7	7.2	8.1	59.9	12.3%
Central African Republic	0.6	0.2	4.3	2.6	0.3	3.0	11.0	2.3%
Chad	0.1	0.0	3.2	1.8	2.1	8.6	15.8	3.3%
Congo	1.5	0.8	0.6	0.8	0.5	0.8	5.1	1%
Democratic Republic of Congo	18.1	5.5	11.9	11.0	1.6	14.0	62.0	12.7%
Equatorial Guinea	0.1	0.1	0.0	0.1	0.0	0.0	0.3	0.1%
Ethiopia	2.6	1.7	2.5	2.2	0.1	8.0	17.2	3.5%
Liberia	1.1	0.5	3.0	2.0	3.7	2.9	13.2	2.7%
Malawi	0.3	0.0	0.7	0.5	2.6	5.3	9.3	1.9%
Nigeria	112.0	1.2	20.5	31.8	45.3	49.3	260.1	53.4%
Sudan and South Sudan[b]	0.0	0.0	0.7	0.4	1.5	4.3	6.9	1.4%
Uganda	0.1	0.0	0.5	0.3	0.5	0.7	2.3	0.5%
United Republic of Tanzania	0.3	0.7	4.6	2.8	2.0	7.7	18.2	3.7%
Total	161.5	17.2	59.8	66.0	68.3	114.0	486.8	100%

[a] These figures are the product of the potential disease burden due to off-target infections in people treated with ivermectin and the assumed effect of ivermectin treatment on the disease burden (see Box 1).

[b] Estimates for Sudan and South Sudan are merged, as information on the burden per capita was reported for the two together (Murray et al. 2012).

Results

We assumed that each year, mass treatment would avert some fraction of the potential disease burden in treated communities. Based on literature, this fraction was assumed to be 0.5 for ascariasis, trichuriasis, strongyloidiasis and EPSDs, 0.2 for hookworm infections, and 0.1 for LF (Box 1).

We estimated that without APOC (counterfactual situation assuming that there is no mass treatment with ivermectin by APOC), the potential disease burden of STH infections, lymphatic filariasis, and EPSD in individuals otherwise treated with ivermectin would amount to a cumulative burden of 1.7 million DALYs between 1995 and 2010. Of these, 487 thousand DALYs were averted by APOC through ivermectin mass treatment (Table 6.2). Most of the DALYs averted by APOC were related to ascariasis (162 thousand) and scabies (114 thousand), followed by LF (68 thousand), strongyloidiasis (66 thousand), and hookworm infection (60 thousand). Only a small part of the burden averted by APOC was related to trichuriasis (17 thousand). Nigeria contributed 53 % of the total averted number of DALYs related to off-target infections (260 thousand of 487 thousand), followed by the DRC (62 thousand or 13 %) and Cameroon (60 thousand or 12 %).

Figure 6.1 shows the results of the sensitivity analyses. Changing individual β_X parameters by 20 % resulted in estimates very similar to the main estimate. Obviously, increasing or decreasing all β_x parameters simultaneously by 20 % resulted in ±20 % deviations from the main estimate of 487 thousand DALYs averted. Assumed no clustering STH and EPSDs in APOC areas ($h_{ix} = 1.0$) or clustering of all infections but LF in all countries ($h_{ix} = 1.5$) resulted in 16 % lower and 18 % higher estimates of total DALYs averted, respectively.

Discussion

The impact of APOC on off-target NTDs has previously been discussed and considered to be important, but difficult to quantify. We estimated that if APOC would not have been there, STH infections, strongyloidiasis, and scabies would have caused a cumulative burden

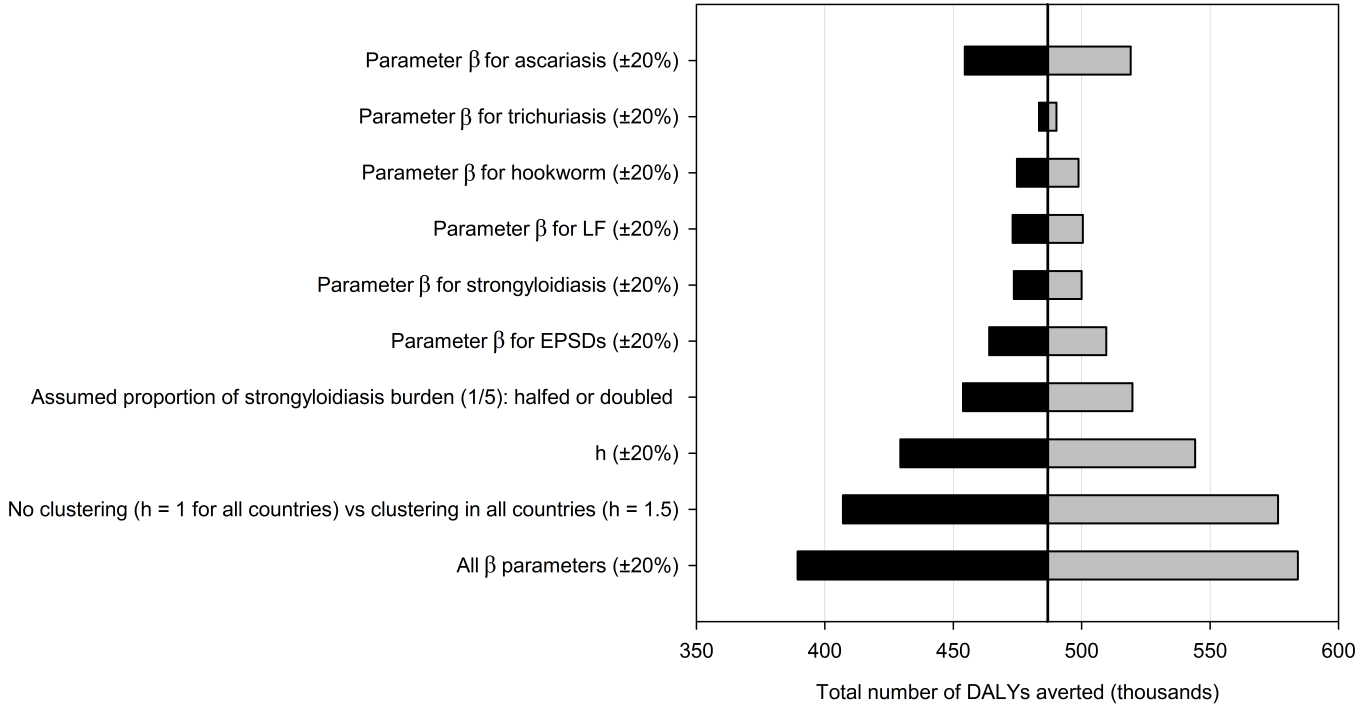

Figure 6.1: Sensitivity analysis for the impact of assumed parameter values on the total averted burden. For each parameter (y-axis), the figure between brackets indicates the relative amount by which it was varied in the sensitivity analysis.

of 1.7 million DALYs lost between 1995 and 2010 in individuals who would otherwise have been treated with ivermectin. We roughly estimated that of these 1.7 million DALYs, mass treatment with ivermectin has averted 500 thousand DALYs. This means that besides the impact of APOC on the burden of onchocerciasis (9 million DALYs averted), there has been an additional 5.5 % health impact through the effect of ivermectin mass treatment on off-target NTDs. This indicates that the cost-effectiveness of APOC is even somewhat higher than previously estimated.

The estimate of 500 thousand additionally averted DALYs was based on a simple approach that included assumptions about the impact of mass treatment on the burden of selected off-target infections endemic in APOC countries. Because we considere a period of six years for estimating the effects of ivermectin mass treatment (i.e. the minimum duration of most APOC programs), our approach may underestimate the averted burden in countries where ivermectin mass treatments have taken place for over six years (i.e. where effects on transmission may be larger). Also, we did not take into account the protective impact of ivermectin mass treatment due to a reduced transmission to children under five years of age and pregnant women (who receive no ivermectin). Gutman et al. (2010) show that the prevalence of some STH infections was significantly lower in pre-school children living in treated communities compared to pre-school children living in non-treated communities. Further, we assumed that APOC interventions have not been accounted for in the burden estimates for off-target NTDs provided by the GBD 2010 study, meaning that at worst (if GBD 2010 does account for APOC), ivermectin mass treatment has had a larger health impact than we estimate here. Also, ivermectin mass treatment probably has an effect on the burden of relatively rare or minor infections that were excluded from our analysis, such as enterobiasis, loiasis, streptocerciasis, serous cavity filariasis, and EPSDs other than scabies. Furthermore, ivermectin mass treatment also has a – yet to be quantified – effect on malaria transmission through the endectocidal effects of ivermectin on Anopheles vectors (Chaccour et al. 2013). On the other hand, we did not consider the burden of severe adverse effects of ivermectin treatment related to loiasis (Boussinesq et al.

2003, 2006), which is endemic in parts of the APOC region (Zouré et al. 2011). Overall, if anything, our results underestimate the true impact of APOC activities on off-target infections.

Our estimates of the impact of APOC on the burden of off-target diseases could be further refined with more sophisticated approaches, such as mathematical modeling. For some of the off-target infections, mathematical models have already been developed, such as for transmission and morbidity due ascariasis (Medley, Guyatt, and Bundy 1993) and transmission of lymphatic filariasis (Stolk et al. 2008). Epidemiological data and understanding of the mechanisms through which parasitic infections cause morbidity in the human host are needed to develop similar models for other parasitic infection, and update currently existing models. However, estimates made with such models are only usefully accurate if they are based on good information about the distribution of worms in host populations. Since such data are not yet widely available and the development of mathematical models is time-consuming and expensive, obtaining more precise estimates of the (averted) burden of off-target infections remains a challenge.

We ignored that in some countries, ivermectin mass treatment is combined with albendazole to target both onchocerciasis and LF (Ottesen et al. 2008). Where this is the case, it is perhaps not justified to fully attribute the estimated effects on off-target diseases to APOC alone. It would be more useful to estimate the overall effect of repeated mass treatments on all target and off-target diseases; such estimates would be larger than the figures presented here, thanks to the addition of albendazole.

The so-called neglected tropical diseases (consisting of STH, filariases, EPSDs, and several other infections) are the most common conditions affecting the poorest 500 million people living in SSA (Hotez and Kamath 2009). The infections covered in our analysis have been estimated to be responsible for a burden of 8.3 million DALYs lost in SSA in 2010 (Murray et al. 2012). Compared to this, our estimate of the health impact of ivermectin mass treatment on off-target diseases is modest. In order to enhance the impact of mass treatment on LF and STH infections, it would be interesting to consider adding albendazole or other STH-specific drugs to mass

treatments (targeting the appropriate age-groups). Guidelines for what anthelminthic drugs should be used in different areas have already been formulated (WHO 2006). To sustain the off-target health impact, it should be considered to continue mass treatments against STH after onchocerciasis (and LF) have been eliminated from APOC target areas; this would also be in line with the London Declaration on Neglected Tropical Diseases.[2]

In conclusion, we roughly estimated that ivermectin mass treatment coordinated by APOC has averted about 500 thousand DALYs related to off-target infections. This health impact constitutes an additional 5.5 % on top of the impact of APOC on the burden of onchocerciasis, and indicates that the cost-effectiveness of APOC is even higher than previously estimated. To amplify and sustain this additional health impact, control programs could consider adding albendazole to mass treatments, and continue this after elimination of onchocerciasis and lymphatic filariasis.

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[2] http://www.unitingtocombatntds.org/endorsements

Chapter 7

Elimination of African onchocerciasis: modeling the impact of increasing the frequency of ivermectin mass treatment

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Abstract

The African Programme for Onchocerciasis Control (APOC) is currently shifting its focus from morbidity control to elimination of infection. To enhance the likelihood of elimination and speed up its achievement, programs may consider to increase the frequency of ivermectin mass treatment from annual to 6-monthly or even higher. In a computer simulation study, we examined the potential impact of increasing the mass treatment frequency for different settings. With the ONCHOSIM model, we simulated 92,610 different scenarios pertaining to transmission conditions, history of mass treatment, and the future mass treatment strategy. Simulation results were used to determine the minimum remaining program duration and number of treatment rounds required to achieve 99 % probability of elimination. Doubling the frequency of treatment from yearly to 6-monthly or 3-monthly was predicted to reduce remaining program duration by about 40 % or 60 %, respectively. These reductions come at a cost of additional treatment rounds, especially in case of 3-monthly mass treatment. We conclude that 6-monthly mass treatment may only be worth the effort in situations where annual treatment is expected to take a long time to achieve elimination in spite of good treatment coverage, e.g. because of unfavorable transmission conditions or because mass treatment started recently. In low coverage settings, first priority should be to increase the treatment coverage rather than increasing frequency. The benefits of increasing mass treatment frequency will be highly dependent on maintained coverage, and could be completely nullified if coverage of mass treatment were to fall in the future.

Introduction

Since 1995, APOC, the African Programme for Onchocerciasis Control has organized annual mass treatment with ivermectin in sixteen endemic African countries, with the aim to control eye and skin disease due to onchocerciasis (Amazigo 2008). Following the first reports of elimination of onchocerciasis from several African savanna foci with mass treatment alone (Diawara et al. 2009; Tekle et al. 2012), APOC has taken up the additional objective of eliminating infection, where possible (APOC 2010). To achieve elimination, it has been suggested that APOC should increase the frequency of mass treatment from annual to 6-monthly, following the example of the Onchocerciasis Elimination Program for the Americas (OEPA), which by means of 6-monthly and 3-monthly mass treatment has rapidly interrupted transmission in the majority of the American foci (Sauerbrey 2008; Cupp, Sauerbrey, and Richards 2011). Shorter and more intensive mass treatment programs are attractive as they speed up elimination, minimize the risk of interruption and emergence of drug resistance, which should be politically appealing to health officials (Stolk et al. 2013). However, increasing the frequency of mass treatment would also require major initial investments from APOC, endemic countries, and Merck, the pharmaceutical company donating ivermectin for onchocerciasis control. Therefore, it is important to carefully evaluate where an increase in frequency is warranted, and where treatment should continue annually.

In most parts of Africa, annual mass treatment has been going on for at least a decade (Coffeng et al. 2013b), and it is not known how and to what extent the remaining program duration would change when switching to a higher mass treatment frequency. The consequences would vary between areas, depending on the local history of control in terms of duration and coverage of mass treatment in the past, and local transmission conditions such as pre-control infection level and inter-individual variation in exposure to fly bites (Winnen et al. 2002). For instance, higher treatment frequencies would be especially useful in reducing program duration (in absolute terms) in areas with high transmission rates and/or a short history of mass treatment.

In the current study, we investigated how increasing mass treat-

ment frequency would affect the remaining program duration and the associated number of mass treatment rounds in African settings. However, findings from past and ongoing African programs based solely on ivermectin mass treatment (Diawara et al. 2009; Tekle et al. 2012) are still too limited and difficult to generalize. Therefore, we performed a computer simulation study with ONCHOSIM, a mathematical model for simulation of onchocerciasis transmission and control (Plaisier et al. 1990; Habbema, van Oortmarssen, and Plaisier 1996). This model has been previously used to predict the effects of onchocerciasis control in Africa (Plaisier et al. 1995, 1997; Winnen et al. 2002; Coffeng et al. 2013b). In the current study, simulations were made based on various combinations of assumptions about transmission conditions; history of mass treatment; frequency, duration, and coverage of future mass treatment rounds; and the effects of ivermectin on adult male and female worms. In particular, we compared the effects of increasing frequency and increasing coverage of mass treatment, as the latter would probably require fewer investments and changes in ongoing programs.

Methods

The simulation model

ONCHOSIM is a micro-simulation model that simulates the life histories of persons and Onchocerca volvulus worms within persons. Simulated individuals are born and die, and are exposed to fly bites, which may transmit O. volvulus larvae from one person to another. ONCHOSIM simulates a closed population, meaning that there is no migration of humans or flies. The probability that an individual is bitten by a fly is assumed to depend on age (between age zero and 20, exposure increases linearly from zero to a personal maximum), sex (women are assumed to experience 30 % fewer fly bites than men), personal factors such as occupation and attractiveness to flies, and the season of the year. Transmitted larvae may develop into adult worms, which in turn produce new larvae or microfilariae (mf) when a person harbors at least one male and one female adult worm. The mf production of adult female worms is assumed to be zero during the worm's first year of life. After this pre-patent period, female worms

are assumed to produce mf at maximum mf production capacity for five years, followed by a linear decline to zero over the course of 15 years (if a female worm lives that long). Adult worms are assumed to have an average reproductive lifespan (including the pre-patent period) of about 10 years, and 95 % of worms are assumed to reach the end of their reproductive lifespan before the age of 13 to 14 years (Plaisier et al. 1991b). More information about quantification of demographic and biological parameters can be found elsewhere (Habbema, van Oortmarssen, and Plaisier 1996).

The probability that a simulated individual participates in mass treatment with ivermectin is governed by age and sex (children under five years of age are not treated; a random proportion of women in reproductive ages is not treated, assuming that they are pregnant or lactating), and a lifelong compliance factor (the higher the factor, the higher the probability that an individual participates in any given treatment round). Some individuals never participate in treatment, because they are chronically ill. More details about he model can be found elsewhere (Habbema, van Oortmarssen, and Plaisier 1996).

Assumptions about settings and future control scenarios

We simulated trends in infections levels for combinations of assumptions regarding settings (transmission conditions, history of mass treatment with ivermectin) and future mass treatment strategy and population coverage (Table 7.1). Assumptions were defined so as to be applicable to areas covered by APOC. Transmission conditions were varied with regard to the average annual biting rate for adult male persons and the amount of inter-individual variation in exposure to fly bites due to personal factors (7 combinations in total). Seasonal variation in biting was assumed to always be proportional to seasonal patterns observed in Asubende, Ghana (Alley et al. 1994). Past and future treatment strategies were defined in terms of number of rounds (315 combinations of 0 to 14 past treatment rounds and 0 to 20 future treatment rounds), mass treatment coverage (7 combinations of maintained, decreasing, or increasing coverage), and frequency (3 options). Simulated mass treatment rounds were scheduled on 1st of July (annual), just prior to the

annual seasonal peak in fly biting rate, or additionally on the 1st of January (6-monthly treatment) and the 1st of April and 1st of October (3-monthly treatment). If the mass treatment program was assumed to switch from annual (past) to 6-monthly or 3-monthly (future) treatment, the new treatment frequency was scheduled to start on the 1st of January of the next year (i.e. six months after the last 'past' treatment), or on the 1st of October of the same year (i.e. three months after the last 'past' treatment), respectively.

Assumptions about ivermectin efficacy

Ivermectin was assumed to instantly kill all mf present in an individual. In addition, we assumed either of two alternative sets of assumptions about the effects of ivermectin on adult worms (Table 7.2). Assumption set 1 has also been used in previous simulation studies (Plaisier et al. 1997; Winnen et al. 2002; Coffeng et al. 2013b), and was quantified such that ONCHOSIM could reproduce trends in skin mf levels as observed in a clinical trial that encompassed five consecutive annual ivermectin treatments (Alley et al. 1994; Plaisier et al. 1995). Assumption set 2 was formulated to reflect evidence of the effects of ivermectin on adult worm survival and reproduction (Duke et al. 1990, 1991a,b, 1992; Chavasse et al. 1993; Kläger et al. 1993; Kläger, Whitworth, and Downham 1996; Gardon et al. 2002; Cupp et al. 2004; Cupp and Cupp 2005), and was quantified such that ONCHOSIM could reproduce trends in worm survival during three years of 3-monthly mass treatment, as estimated from nodulectomy data (Cupp and Cupp 2005), and trends in skin mf levels up to two years after a single dose of ivermectin as reported in a published meta-analysis (Basáñez et al. 2008). Model parameter values for ivermectin efficacy were fitted to the data with maximum likelihood, using the mean output of 100 repeated ONCHOSIM simulations as expected values. Figure 7.1 illustrates example predictions for the effects of ivermectin on population infection levels, based on assumption sets 1 and 2.

Table 7.1: Setting characteristics and treatment scenarios for simulations. For each combination of the listed factors, we estimated the probability of elimination (zero prevalence of infection) 50 years after the last mass treatment, based on 1,000 repeated simulations in ONCHOSIM.

Settings and scenarios	Possible values
Setting: transmission conditions	
Seasonality	Year-round transmission[a]
Pre-control CMFL (community microfilarial load, the geometric mean microfilarial load in people of age 20 and above)	5, 10, 30, 55, 80 microfilariae per skin snip, corresponding to mf prevalence levels ranging from $\sim 45\,\%$ to $\sim 85\,\%$, or 9,400 to 22,200 fly bites per male person per year
Inter-individual variation in relative exposure to fly bites related to personal factors (e.g. attractiveness and occupation)	Low or high, specified as a gamma distribution for relative exposure to fly bites with mean value 1 and scale 3.5 or 1.0, respectively[b]
Setting: history of control	Annual
Past mass treatment frequency	0, 1, 2, ..., 14
No. of mass treatment rounds provided until present	Coverage low (50 %), intermediate (65 %), or high (80 %)
Coverage in past mass treatment rounds (% of total population)	
Scenario: future mass treatment	
Future mass treatment frequency	Annual, 6-monthly, or 3-monthly
No. of future mass treatment rounds	0, 1, 2, ..., 20, allowing estimation of the minimum number of future treatment rounds needed to achieve 99 % probability of elimination
Coverage of future mass treatment rounds	Stable coverage (same as in the past), 15 % lower (only for past coverage levels of 65 % and 80 %), or 15 % higher (only for past coverage levels of 50 % and 65 %)

[a] Seasonality of fly biting rates was assumed to be proportional to the seasonal pattern observed in Asubende, Ghana (Alley et al. 1994); the monthly biting rates (January–December) were assumed to be 104 %, 91 %, 58 %, 75 %, 75 %, 66 %, 102 %, 133 %, 117 %, 128 %, 146 %, and 105 % times the average monthly biting rate.

[b] Low variance in relative exposure was combined with all possible values for pre-control CMFL. High variance in exposure was only combined with pre-control CMFL of 5 and 10 microfilariae per skin snip; assuming that for highly endemic areas individual variation in exposure to fly bites is not very high because of the multitude of flies (i.e. everyone is bitten very often).

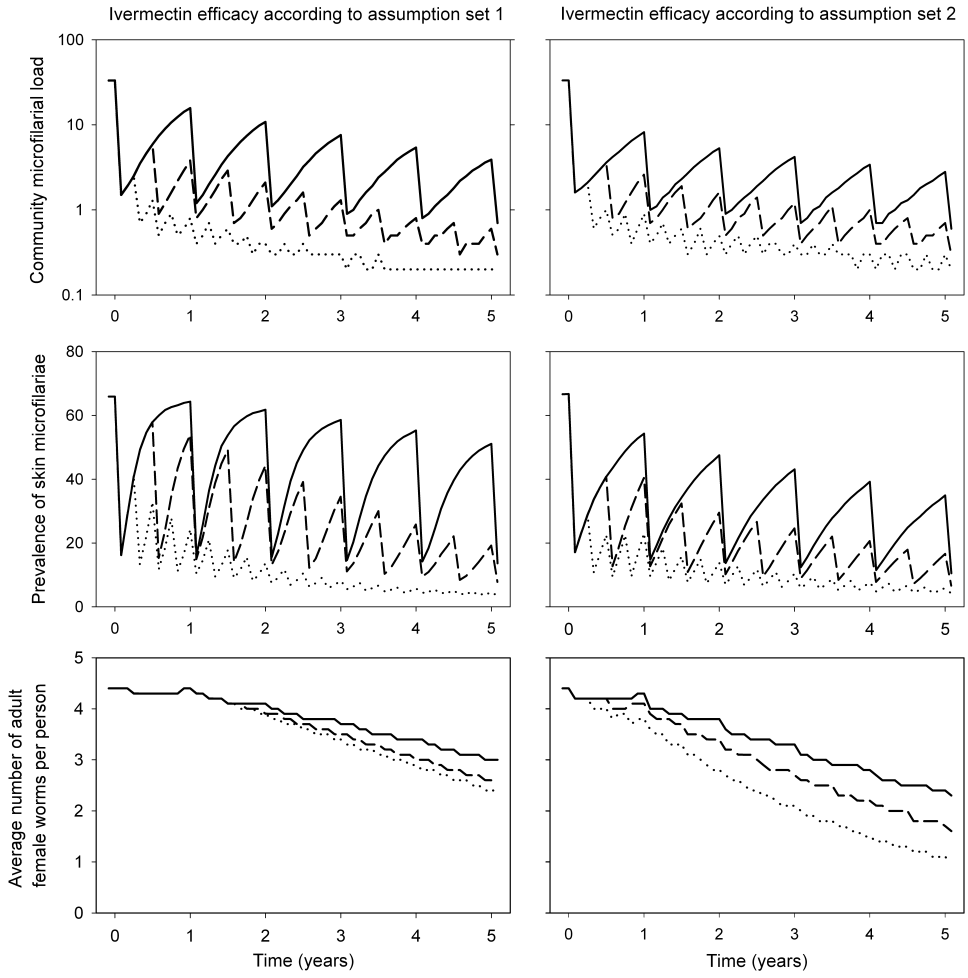


Figure 7.1: ONCHOSIM predictions for community infection levels, based on two sets of assumptions about ivermectin efficacy. Ivermectin was assumed to instantly kill all mf present in an individual. In addition, we assumed either of two alternative sets of assumptions about the effects of ivermectin on adult worms (left and right panels; for details see Table 7.2). The frequency of ivermectin mass treatment was assumed to be either annual (solid lines), 6-monthly (dashed lines), or 3-monthly (dotted lines). The trends depicted here are the averages of 100 simulations of a hypothetical village with 400 inhabitants and a pre-control community microfilarial load of 30 microfilariae per skin snip. Ivermectin mass treatment was assumed to cover 65 % of the population ($\sim$ 80 % of eligible population).

Table 7.2: Two sets of assumptions about ivermectin efficacy in ONCHOSIM.

	Assumption set 1	Assumption set 2
Microfilaricidal effect	100 %, instantaneous upon administration.	100 %, instantaneous upon administration
Macrofilaricidal effect	None.	Each treatment kills 6 % of female adult worms and 12 % of male adult worms.[a] Pre-patent worms are not affected.
Temporary halt in production of microfilariae	All female worms temporarily stop producing mf. Production recovers gradually over time in all worms, reaching maximum production capacity after 11 months on average.[b]	Only female worms that were producing mf at the time of treatment temporary stop producing mf. Production is resumed at full capacity after a random amount of time.[c]
Permanent reduction in adult female worm capacity to produce microfilariae	35 % reduction per treatment, cumulative effects allowed	None.

[a] Excess mortality due to ivermectin was allowed to differ between male and female worms, reflecting the relative absence of male worms from subcutaneous nodules after repeated ivermectin treatment (Duke et al. 1990, 1991a,b, 1992; Kläger, Whitworth, and Downham 1996; Gardon et al. 2002; Cupp et al. 2004; Cupp and Cupp 2005). The macrofilaricidal effects of ivermectin were allowed to vary per treatment; however, this variation could not be estimated from the aggregated data (Cupp and Cupp 2005). Instead, we arbitrarily assumed beta distributions with mean 6 % (2.5 % and 97.5 % percentiles 1.3 %–14.0 %) and 12 % (3.9 %–19.0 %), with the macrofilaricidal effects on male and female worms being perfectly correlated.

[b] This treatment effect was assumed to vary per worm and treatment; 2.5 % and 97.5 % percentiles 2–24 months.

[c] This assumption represents the notion that ivermectin causes temporary congestion of female worm uteri with dead mf, effectively preventing insemination and release of microfilariae (Chavasse et al. 1993; Kläger et al. 1993). Time until recovery was assumed to vary per worm and treatment, and to follow an exponential distribution with mean 3.5 years (fitted to data; Basáñez et al. 2008). This implies that 5 % of adult female worms can be inseminated and release microfilariae within two months after exposure to ivermectin. Likewise, congestion resolves in 25 %, 50 %, 75 %, and 95 % of adult female worms within 1, 2.5, 5, and 10.5 years after exposure to ivermectin, respectively.

Simulation

Because many processes simulated in ONCHOSIM involve probabilities, repeated model simulations based on the same assumptions will results in slightly different predictions because of stochastic variation. We estimated the probability of elimination, based on the fraction of 1,000 repeated simulations that result in elimination. Elimination was defined as absence of infection 50 years after the last mass treatment. Infection diagnosis was based on two skin snips per person. The long time lap in the definition of elimination accounts for the fact that after some number of mass treatment rounds, infection may spontaneously disappear over time through natural attrition of the remaining worm population, even though there is still infection present shortly after the suspension of mass treatment. Probability of elimination was thus estimated for each combination of assumptions (92,610 in total), assuming a hypothetical village with 400 inhabitants (a village size typical for rural Africa). For every combination of transmission setting, history of control, future control strategy, and ivermectin efficacy (4,410 combinations), we determined the minimum number of future treatment rounds required to achieve $\geq 99\,\%$ probability of elimination, if possible within the simulated range of 0 to 20 future treatment rounds. The associated remaining program duration was calculated by dividing the number of future treatment rounds by the future treatment frequency per year. Simulations were performed on the Dutch Life Science grid[1], a UNIX-based computer grid network shared between several Dutch universities and academic institutes. Simulation results were processed in R (version 2.13.2).

Results

Figure 7.2 shows ONCHOSIM-predicted trends in mf prevalence and illustrates how the probability of elimination is estimated. This figure represents a setting where ten annual treatment rounds took place in the past (before time 0) and treatment is not continued into the future. After each mass treatment, the model predicts a

[1] http://www.surfsara.nl/project/life-science-grid

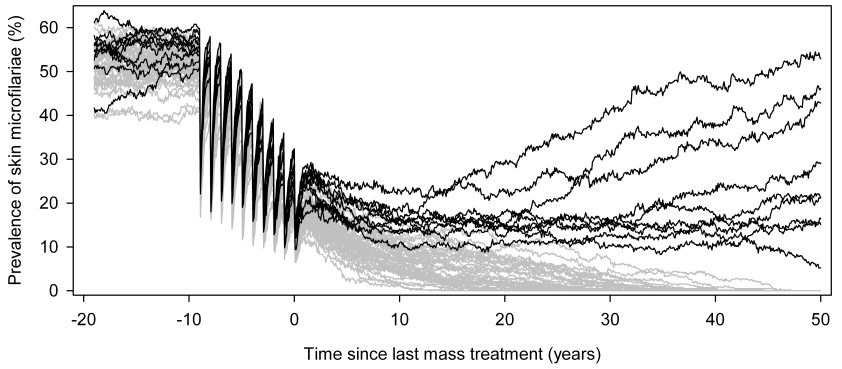


Figure 7.2: Example prediction for the prospect of elimination, generated by ONCHOSIM. The graph shows expected trends for a setting with 10 past annual treatment rounds at 65 % population coverage, and treatment is not continued into the future. Time 0 represents the current situation and the last treatment was given just before time 0. We assumed a pre-control community microfilarial load of about 10 mf per skin snip, which is equivalent to a crude prevalence of skin microfilariae of about 50 %; low variation between individuals in relative exposure to fly bites; and ivermectin efficacy according to assumption set 1 (Table 7.2). Each of the 50 lines represents a single simulation of a typical rural village population in Africa (about 400 individuals). Graph line colors indicate whether a simulation contained individuals with detectable skin microfilariae 50 years after the last mass treatment (black lines, $n = 9$), or not (grey lines, $n = 41$). In this example, the probability of elimination is $41/50 = 82\%$. The erratic appearance of the graph lines is due to the stochastic nature of the simulations.

strong immediate drop in mf prevalence, followed by a rapid recovery. Overall, however, there is a gradual decline in mf prevalence and this continues after the tenth round, even without further treatments. The figure illustrates that to achieve elimination, it is not necessary to clear all infection before mass treatment can be stopped; after a sufficient number of mass treatment rounds, infection levels dwindle further, with the possibility of causing elimination by natural attrition of the worm population. In this example, 41/50 simulations resulted in elimination, yielding 82 % probability of elimination.

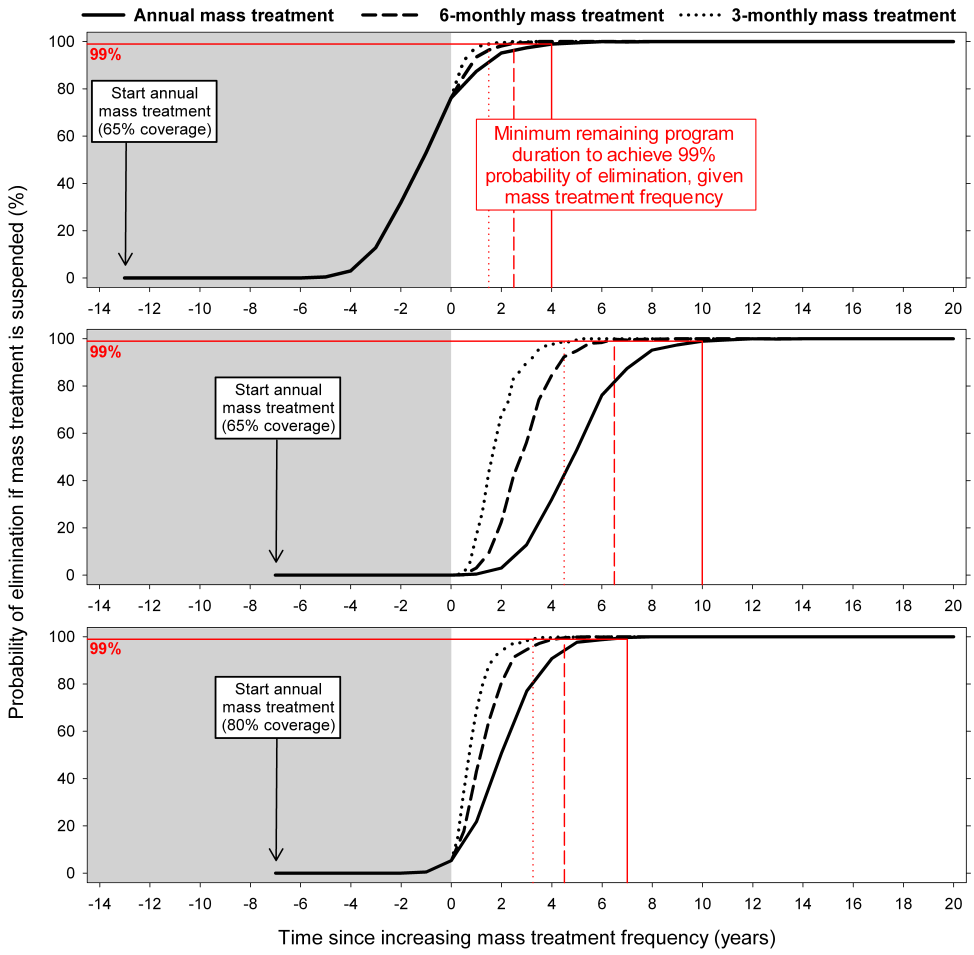
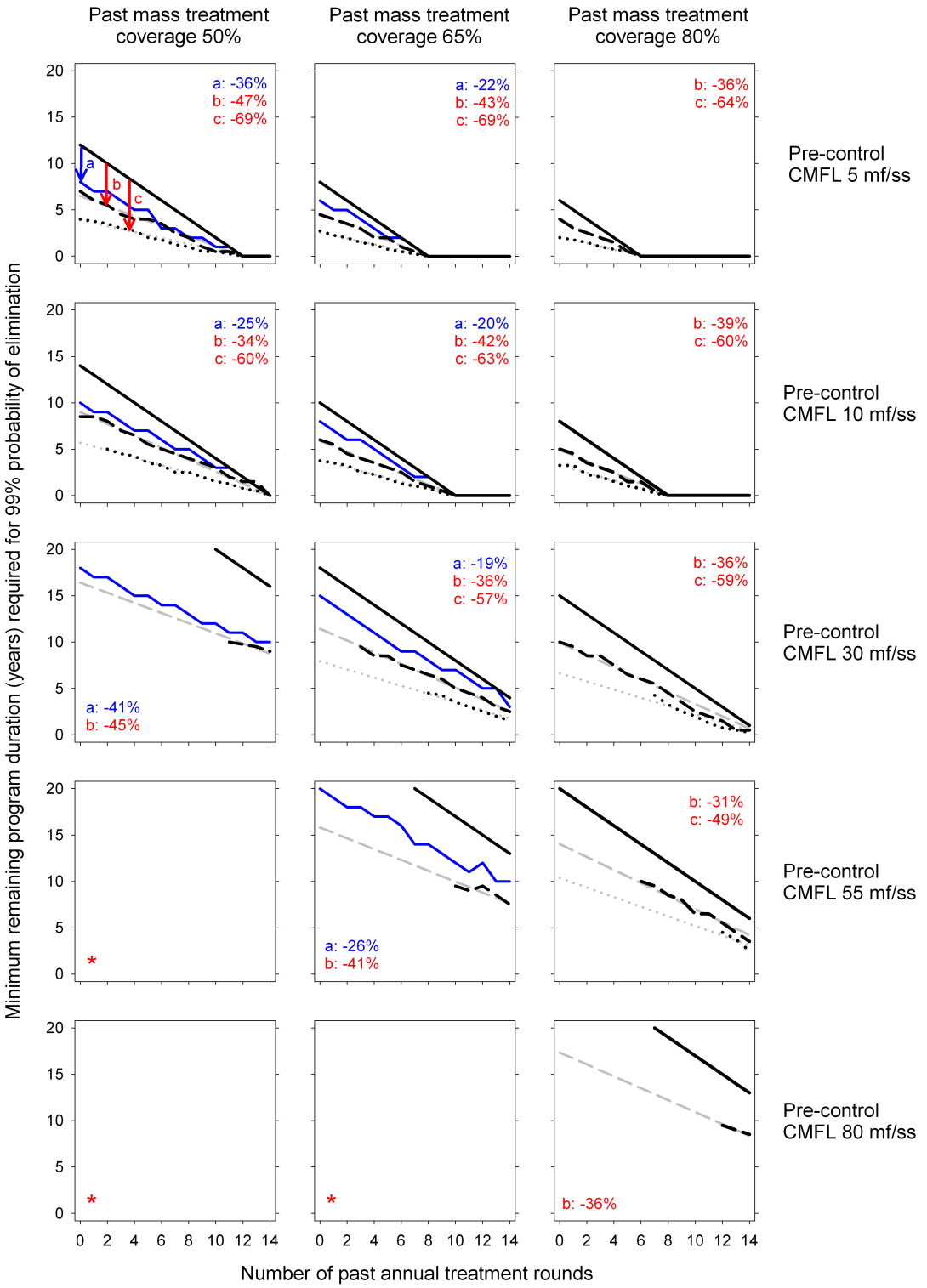


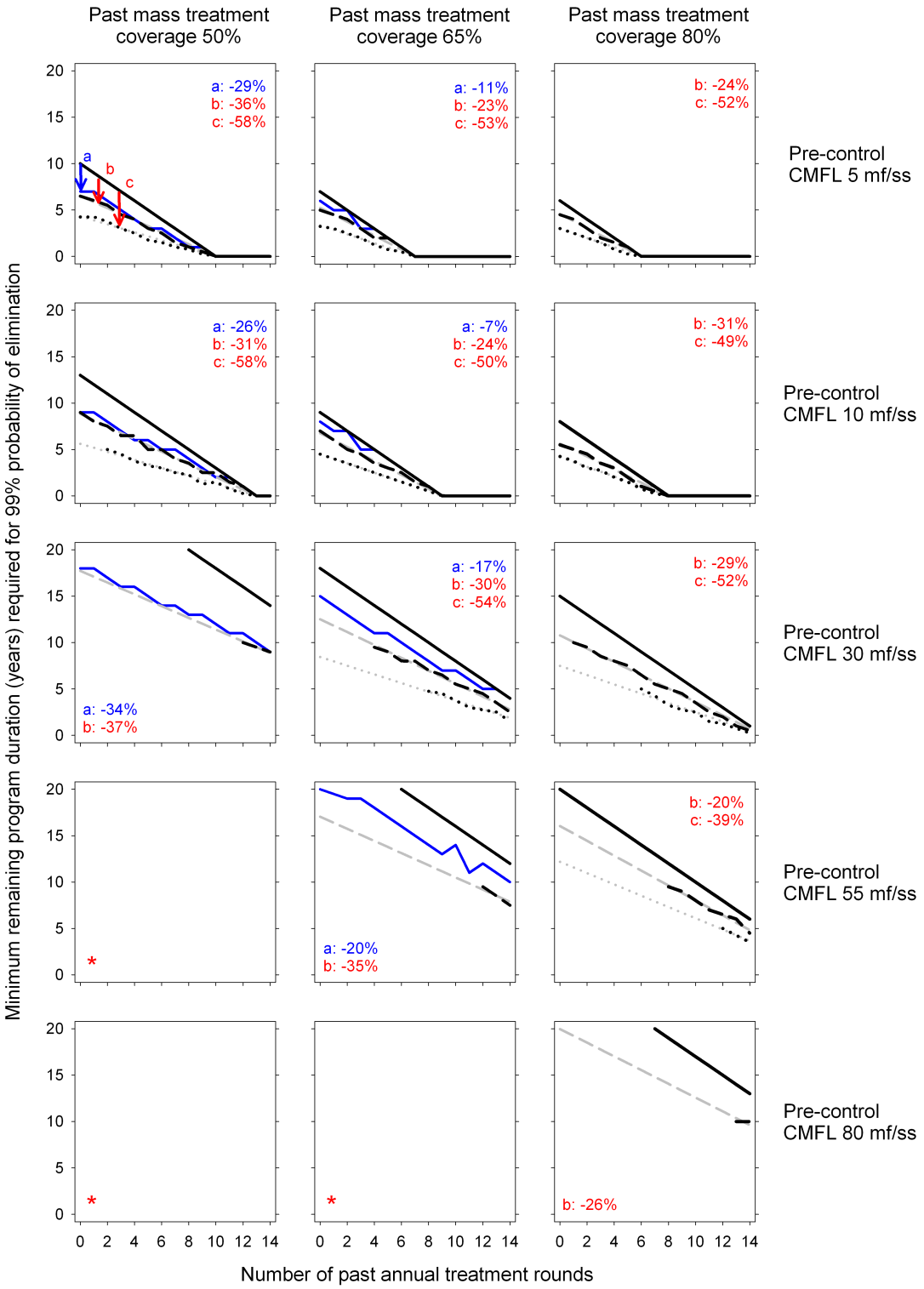
Figure 7.3: Predicted trends in probability of elimination over time for settings with different history of control. The three panels represent predictions for different histories of control in terms of number of past treatment rounds (14 or 8) and mass treatment coverage (65 % or 80 %). Black lines represent the probability of elimination (y-axis) if mass treatment were to be suspended at a certain point in time (x-axis). Trends until now (time 0) are displayed against a shaded background, while expected future trends are shown against a white background. Different line types pertain to different future mass treatment frequencies (annual, 6-monthly, or 3-monthly). Red lines highlight the predicted minimum remaining program duration required to achieve 99 % probability of elimination (based on 1,000 repeated simulations). The three panels are equal with respect to assumed transmission conditions (pre-control community microfilarial load of about 30 mf per skin snip, low variation between individuals in relative exposure to fly bites) and ivermectin efficacy (assumption set 1). Elimination was defined as absence of infection 50 years after suspension of mass treatment.

Figure 7.4: (Following three pages.) Predicted minimum remaining program duration required until elimination of onchocerciasis. Subfigures (a) through (d) pertain to different assumptions about ivermectin efficacy (assumption set 1 or 2) and inter-individual variation in relative exposure to fly bites (low or high). Graphs illustrate the minimum remaining program duration (y-axis) required for 99 % probability of elimination (absence of infection 50 years after the mass last treatment), given the number of annual mass treatment rounds already completed (x-axis), as predicted by ONCHOSIM (1,000 simulations per scenario). Each graph compares four strategies: continuing annual mass treatment at same coverage (solid black line), switching to 6-monthly mass treatment at same coverage (dashed black line), switching to 3-monthly mass treatment at same coverage (dotted black line), or continuing annual treatment at increased coverage (+15 percentage points; solid blue line; only for past mass treatment coverage of 50% and 65%). Within each subfigure, different panels pertain to increasing pre-control infection levels (top to bottom), and increasing values of past mass treatment coverage (left to right). Grey lines represent linear extrapolations of simulated data, fitted such that they intersect with the x-axis at the same point as graph lines for annual mass treatment (black solid lines). Values in the corner of each panel represent reductions in remaining program duration, when increasing coverage (a), switching to 6-monthly mass treatment (b), or switching to 3-monthly mass treatment (c), compared to continuing annual treatment at the same coverage. Panels marked with an asterisk (*) pertain to simulations that did not result in 99 % probability of elimination within 20 future treatment rounds, and hence contain no graph lines.



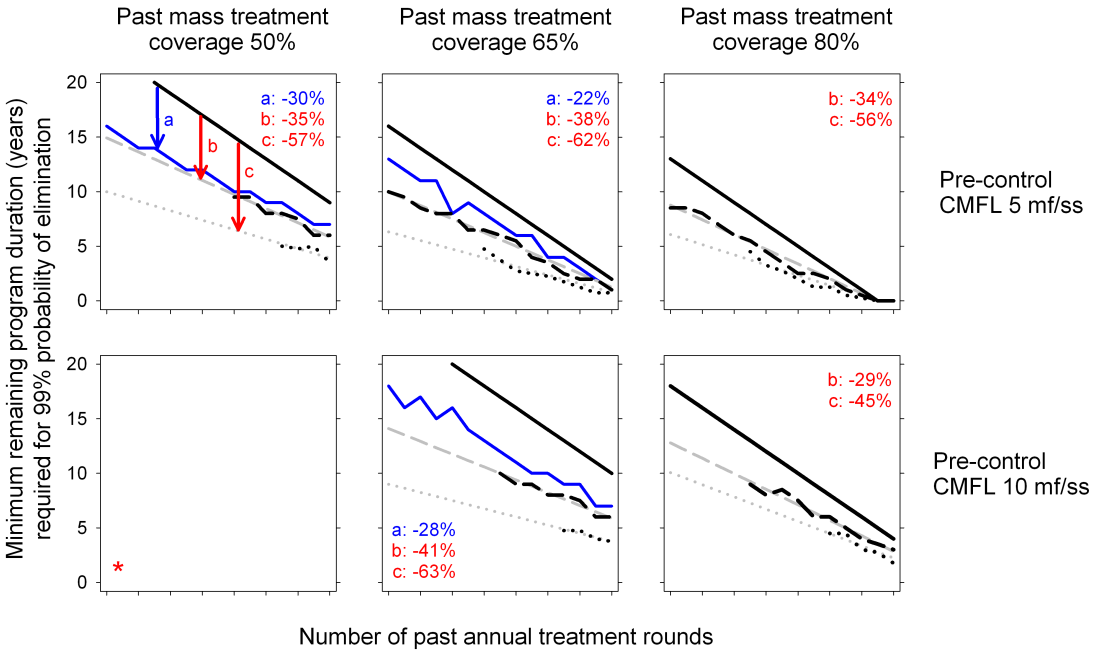
(a) Ivermectin efficacy as in assumption set 1 and low inter-individual variation in relative exposure to fly bites.

Figure 7.4: See previous page for caption. Figure continues on next page.

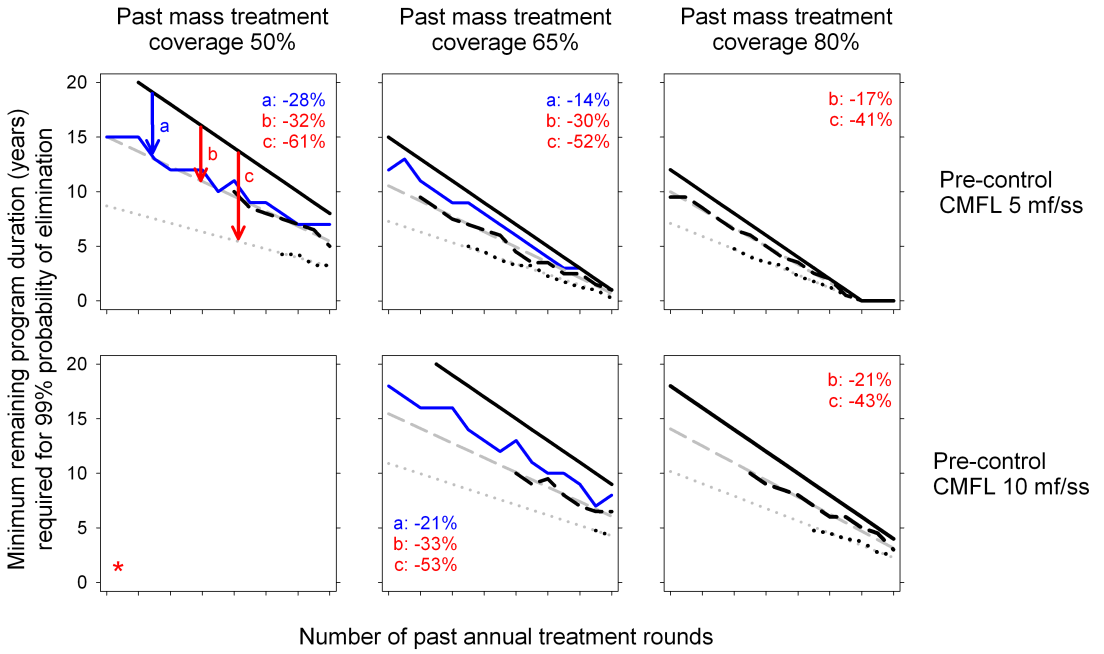


(b) Ivermectin efficacy as in assumption set 2 and low inter-individual variation in relative exposure to fly bites.

Figure 7.4: Continued.



(c) Ivermectin efficacy as in assumption set 1 and high inter-individual variation in relative exposure to fly bites.



(d) Ivermectin efficacy as in assumption set 2 and high inter-individual variation in relative exposure to fly bites.

Figure 7.4: Continued.

Table 7.3: Effects of future control strategy on remaining program duration and treatment rounds until elimination. All differences are defined compared to the strategy of continuing annual treatment strategy at maintained treatment coverage, and are based on the assumptions of low variation in exposure to fly bites. For details about assumptions regarding ivermectin efficacy (assumption sets 1 and 2), see Table 7.2.

Mass treatment strategy			Ivermectin assumption set 1		Ivermectin assumption set 2	
Past coverage	Future coverage	Future frequency	Program duration	Number of treatment rounds	Program duration	Number of treatment rounds
50%	50%	6-monthly[a]	−41%	+18%	−34%	+32%
		3-monthly[a]	−64%	+43%	−58%	+69%
	65%	annually[a]	−37%	−37%	−32%	−32%
		6-monthly[a]	−60%	−21%	−36%	+28%
		3-monthly[a]	−75%	0%	−77%	−7%
65%	50%	6-monthly[b]	−14%	+72%	−3%	+95%
		3-monthly[b]	−46%	+118%	−32%	+151%
	65%	6-monthly[a]	−40%	+21%	−29%	+42%
		3-monthly[a]	−62%	+51%	−52%	+92%
	80%	annually[a]	−23%	−23%	−17%	−17%
		6-monthly[a]	−48%	+4%	−12%	+76%
		3-monthly[a]	−69%	+26%	−69%	+23%
80%	65%	6-monthly[b]	−25%	+50%	−15%	+69%
		3-monthly[b]	−52%	+91%	−46%	+118%
	80%	6-monthly[a]	−35%	+31%	−26%	+48%
		3-monthly[a]	−59%	+66%	−49%	+103%

[a] Estimates were similar for different assumptions about pre-control levels of infection and number of past treatment rounds.

[b] Reductions in program duration tended to be smaller for settings with fewer past treatment rounds and higher pre-control infection levels (and vice versa). Analogously, the increase in remaining number of mass treatment rounds tended to be higher for settings with fewer past treatment rounds and higher pre-control infection levels (and vice versa).

Figure 7.3 illustrates how the probability of elimination (y-axis) increases with program duration (x-axis); the program stops when the elimination probability reaches 99 % (red drop-down lines). This figure shows how increasing mass treatment frequency from now on (time = 0) would reduce the remaining program duration required. In the top panel, for example, a shift from annual to 6-monthly treatment would reduce the remaining program duration from 4 to 2.5 years (37.5 % reduction). This reduction is associated with an increase in the remaining number of mass treatment rounds from 4 to 5 (2 rounds per year × 2.5 years; 25 % increase). In general, the longer the expected remaining program duration under annual treatment, the larger the absolute reduction achieved by shifting from annual treatment to higher frequency treatment. Thus, the impact of increasing mass treatment frequency on remaining program duration was larger if mass treatment started more recently (Figure 7.3, middle vs. top panel) and when mass treatment coverage was lower (middle vs. bottom panel). Similarly, the time reduction would be larger in settings with more unfavorable transmission conditions (e.g. high pre-control infection levels and/or high variation in relative exposure to fly bites).

Figure 7.4 shows the minimum remaining program duration required for 99 % probability of elimination (y-axis), in relation to the number of (annual) mass treatment rounds already completed (x-axis), and the future mass treatment strategy. Assuming low variation in relative exposure to fly bites and ivermectin efficacy as in assumption set one (Figure 7.4a), a shift from annual to 6-monthly treatment reduces the remaining program duration by about 40 %. This is more or less independent of setting characteristics (number of treatment rounds already provided, average coverage, pre-control endemicity level). The reduction is always less than 50 %, implying that the number of treatment rounds always increases. The figure also shows the effect of increasing treatment coverage instead of frequency (blue lines). Increasing coverage of annual mass treatment from §50% to 65 % causes a reduction in the remaining program duration, similar in magnitude to the reduction achieved by increasing the frequency to 6-monthly (left column of panels). In contrast to increasing frequency, increasing coverage also causes a reduction in

the remaining number of treatment rounds. In settings with higher coverage levels, a further increase in coverage has a smaller impact on remaining duration (middle column of panels). Predictions based on ivermectin efficacy as in assumption set 2 (Figure 7.4b) were similar to those based on assumption set 1 (Figure 7.4a). Only predictions for annual treatment were slightly more optimistic (1–2 years shorter program duration) when based on assumption set 2. As expected, high inter-individual variation in exposure to fly bites was associated with longer program duration required for elimination (Figure 7.4c and Figure 7.4d). Still, the relative differences between future mass treatment strategies were similar to those based on the assumption of low inter-individual variation in exposure to fly bites.

Table 7.3 shows the relative reduction in remaining program duration resulting from a change in treatment frequency or treatment coverage. The table also shows the associated change in remaining number of treatment rounds. Reductions in program duration were highest for situations where past mass treatment coverage was relatively low, and vice versa. Whereas increasing coverage only was always associated with a reduction in the number of mass treatment rounds, switching to high frequency mass treatment was associated with an increase in number of mass treatment rounds, except when coinciding with an increase in coverage. Further, if switching to high frequency mass treatment would coincide with a drop in coverage of 15 percentage points (e.g. due to perceived lower importance of participation among the target population), this strongly attenuated (and sometimes even completely nullified) the reduction in the program duration, and would lead to a further increase in the number of future treatment rounds required. All aforementioned patterns were more pessimistic for predictions based on the assumption of ivermectin efficacy according to assumption set 2 (lower reduction in program duration, higher increase in number of treatment rounds; rightmost two columns of Table 7.3).

Discussion

With the mathematical simulation model ONCHOSIM, we predicted how a shift from annual to 6-monthly or 3-monthly ivermectin mass treatments changes remaining program duration and number of mass treatment rounds required for 99 % probability of elimination. We predicted that high frequency mass treatment at maintained coverage will reduce duration until elimination by as much as 40 % (6-monthly mass treatment) or 64 % (3-monthly mass treatment), though always at a cost of additional treatment rounds. In low coverage settings, reductions in remaining program duration can be achieved just as well by increasing treatment coverage as by increasing treatment frequency to 6-monthly. Further, while an increase in both frequency and coverage of mass treatment would work synergistically and could in some settings even decrease the number of mass treatment rounds required for elimination, a drop in coverage could strongly attenuate or even completely nullify the reduction in program duration, especially in areas with high levels of residual infection and high potential for transmission.

Our results were generated using computer simulation, as empirical evidence from past and ongoing programs in Africa based solely on ivermectin mass treatment is still limited and difficult to generalize (Diawara et al. 2009; Tekle et al. 2012). An important uncertainty concerns the efficacy of ivermectin treatment on adult worms. We compared two sets of assumptions regarding ivermectin efficacy. Based on either assumption set, ONCHOSIM could adequately reproduce published trends in infection levels (Diawara et al. 2009) during 15 years of ivermectin mass treatment observed in the River Gambie (6-monthly mass treatment) and River Bakoye foci (annual mass treatment) in West Africa (unpublished). Also, in terms of program duration required for elimination, results were similar for the two assumption sets. Only the benefits of increasing frequency were lower when based on assumption set 2, as annual mass treatment was slightly more effective than when based on assumption set 1. A point of uncertainty is that in assumption set 2, we assumed that the macrofilaricidal effect of ivermectin is independent of treatment frequency, which may not be the case (Duke et al. 1991b, 1992; Cupp et al. 2004). If in reality, the macrofi-

laricidal effects increase with treatment frequency, the benefits of high frequency mass treatment may be larger than presented here. Therefore, it is important that our results be compared to future field data regarding elimination of African onchocerciasis.

Other minor uncertainties in our predictions concern the fact that ONCHOSIM is currently parameterized and calibrated to reproduce transmission dynamics in savanna areas, whereas a large part of the APOC region is covered by forest with other parasite-vector-complexes (Coffeng et al. 2013b). Also, we assumed no migration of infected flies or humans, an assumption which may not always hold, especially in settings of civil unrest, and in savanna areas where flies may travel long distances on the wind (Dadzie, Neira, and Hopkins 2003). Therefore, our model predictions may differ somewhat from situations in the field. Nevertheless, we expect that our general conclusions hold.

The effects of frequency and coverage of mass treatment on prospects of elimination have been previously studied with ONCHOSIM by Winnen et al (Winnen et al. 2002). However, the current study considers more settings and scenarios, and accounts for the fact that in large parts of Africa, onchocerciasis control has been ongoing for some time. Further, the current study provides more precise estimates of the prospects of elimination, based on 1,000 simulation per scenario. Winnen et al concluded that duration until elimination of a program based entirely on 6-monthly mass treatment would be less than half that of a program based entirely on annual treatment. In light of our predictions, this now seems too optimistic.

Compared with annual mass treatment, high frequency mass treatment is more resource-demanding, due to costs related to its implementation, logistics, and extra mass treatment rounds. It may seem attractive to increase mass treatment frequency in projects performing poorly (low coverage). However, according to our simulations, increasing coverage can be just as effective as increasing frequency of mass treatment (especially in low coverage settings), while being less resource-demanding, requiring fewer mass treatment rounds, and most likely, fewer investments in the supply chain. Switching to 6-monthly mass treatment may only be worth the ef-

fort in situations where annual treatment is expected to take a long time to achieve elimination in spite of good treatment coverage, e.g. because of unfavorable transmission conditions or because mass treatment started recently. Increasing the frequency to 3-monthly seems very unattractive as it may lead to doubling of the number of treatment rounds required for elimination. In contrast, increasing both coverage and frequency, if feasible, may even reduce the remaining number of mass treatment rounds required until elimination. Whether this results in cost savings depends entirely on the investments required for implementing alternative future mass treatment strategies. Therefore, there is a need for cost projections for annual and high frequency mass treatment, similar to those developed for lymphatic filariasis (Stolk et al. 2013).

There are several requirements and barriers for the implementation of high frequency mass treatment. First, adequate planning is required to guarantee sufficient drug supplies. Second, communities targeted for high frequency mass treatment would have to be sensitized, as in Africa, ivermectin mass treatment has been implemented using a community-directed approach (Amazigo 2008). Third, high frequency mass treatment would have to be harmonized with ongoing integrated control of onchocerciasis and other tropical diseases (Dembélé et al. 2012; Mwinzi et al. 2012). Further, implementation of high frequency mass treatment may be difficult because of heavily burdened countries' health systems (Coulibaly et al. 2008), and community volunteers. Also, high frequency mass treatment may not be feasible everywhere due to weather, seasonal migration of populations, logistical considerations.

African onchocerciasis elimination programs could base their choice of future mass treatment strategy on a time horizon, e.g. the goal to achieve elimination in 2025. Such a time horizon is attractive for advocacy, and allows programs to evaluate what future mass treatment strategy would allow them to achieve elimination within the specified timeframe, with the minimum demand of resources. However, such a timeframe might also lead to choosing high resource-demanding mass treatment strategies, whereas elimination might also be achieved with fewer resources and somewhat more time.
Conclusion

In Africa, shifting to 6-monthly mass treatment with ivermectin will shorten the program duration required for onchocerciasis elimination. The associated increase in the remaining number of mass treatment rounds is probably worth the effort in settings where annual treatment may be expected to still take a long time to achieve elimination in spite of good coverage, e.g. because of unfavorable transmission conditions or because mass treatment started recently. In low coverage settings, priority should be given to increasing mass treatment coverage, as this is a less resource-demanding option that is similarly effective. The benefits of increasing mass treatment frequency will be highly dependent on maintained coverage, and could be completely nullified if coverage were to fall after increasing mass treatment frequency.

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Chapter 8

General discussion

Answers to the research questions

What was the pre-control disease burden of onchocerciasis in Africa?

In **Chapter 4** (Coffeng et al. 2013b), we report that in 1995, prior to the initiation of ivermectin mass treatment, the total population in areas covered by the African Programme for Onchocerciasis Control (APOC) constituted about 72 million individuals. Of these, about 32 million were infected with at least one adult female *Onchocerca volvulus* worm (45 %), 400 thousand were blind (0.6 %), 900 thousand were visually impaired (1.2 %), and 10 million suffered from troublesome itch (14 %) due to onchocerciasis. The associated disease burden (**Chapter 5**), expressed in disability adjusted life years (DALYs), was estimated at 1.7 million DALYs lost in 1995 (23.1 DALYs per 1,000 persons in APOC target areas): 1,102,000 DALYs related to troublesome itch, 523,000 DALYs from blindness (including premature mortality due to blindness), and 29,000 DALYs due to visual impairment.

A major improvement over previous estimates of the pre-control disease burden of onchocerciasis (Remme 2004) is that the estimates presented here are based on representative field data on pre-control infection levels, whereas previous estimates were based on national registry data, which are known to be incomplete and often underestimate the true disease burden. However, the burden of disfiguring skin disease should still be added to our estimates, especially given that skin disease is more prevalent than eye disease, and according to the recently published updated disability weights, may cause considerable disability (disability weights for different symptoms of disfiguring skin disease range between 0.013 and 0.562, compared to 0.195 for blindness; **Chapter 5**; Salomon et al. 2012).

Our estimate of the pre-control disease burden of onchocerciasis in APOC target areas was derived from systematically collected data on pre-control prevalence of onchocercal nodules in adult males. This derivation involved translating nodule prevalence in adult males to prevalence of skin microfilariae (mf) in the general population, based on a simple rule of thumb (Figure B.2; Remme 2004). According to this approach, nodule prevalences in adult males of 20 % and 40 %

are equivalent to mf prevalences in the general population of 40 % and 60 %, respectively. These translations were in line with results of the more sophisticated analysis of the association between nodule to mf prevalence, presented in **Chapter 2** (Coffeng et al. 2013a), which take into account sampling variation and misclassification due to imperfect specificity of the nodule palpation method. Though the simpler approach applied in **Chapter 4** does not account for these factors, the translation of nodule to mf prevalence should have been accurate enough to predict mean levels of infection and associated morbidity in APOC areas with reasonable precision. Misclassification bias due to low specificity of nodule palpation is relevant for low and non-endemic areas and may therefore have caused a slight inflation of our estimate of the disease burden in hypoendemic areas (nodule prevalence in adult males $< 20\,\%$). However, this bias should be limited as morbidity levels are disproportionally low in hypoendemic areas (compared with mesoendemic and hyperendemic areas), and therefore the 'true' disease burden should lie well within the range of estimates provided by the multivariate sensitivity analysis presented in **Chapter 4**. The more sophisticated model for translation of nodule to mf prevalence presented in **Chapter 2** is relevant when predictions are made for smaller geographic areas, i.e. when measurement error and geographical variation in the association between nodule and mf prevalence play a relatively large role. In such cases, the associated uncertainty should be carried through into the predictions, which can be done as described in **Appendix A**.

In **Chapter 3** (Coffeng et al. 2012), we report patterns in the joint occurrence of onchocercal eye and skin disease in individuals, and discuss implications for estimating the disease burden of onchocerciasis. Adding up the burden of separate symptoms in an individual may lead to overestimation of the disease burden, as the individual burden of a symptom may be modified by the presence of a second symptom (Murray and Lopez 2000). We found considerable concurrence of skin depigmentation and vision loss, and concurrence of troublesome itch and reactive skin disease. To prevent overestimation of the disease burden, we proposed to classify symptoms in three groups based on the mechanics by which they incur a disease burden: functional impairment (vision loss), discomfort (trouble-

some itch), and stigma (disfiguring skin disease). We argued that due to the different underlying mechanisms, the burden of these three separate groups of symptoms may be added up without gross over- or underestimation of the disease burden. This approach was taken in **Chapter 4** (Coffeng et al. 2013b) and **Chapter 5**, though only eye disease and troublesome itch were considered there.

The recently published Global Burden of Disease (GBD) 2010 Study (Murray et al. 2012) reports estimates of the global burden of onchocerciasis (including Central and West Africa, Latin America, and Yemen). These estimates were based on a simulation exercise similar to that described in **Chapter 4** (Coffeng et al. 2013b), performed by the author and a team of colleagues from Erasmus MC Rotterdam, Imperial College London, IRD France, and independent experts. It was estimated that in 1990, about 1.8 million people were visually impaired and 730 thousand were blind due to onchocerciasis in the whole of Africa, with about half of the prevalent cases living in areas covered by the Onchocerciasis Control Program (OCP), and the other halve living in areas later covered by APOC. New cases of blindness occurred most in future APOC areas (40 thousand vs. 12 thousand in OCP areas). Furthermore, it was estimated that about 14 million people in Africa (12 million in future APOC areas) suffered from some kind of onchocercal skin disease with or without itch (as defined by Murdoch et al. (1993)), with about 2.2 million (1.8 million in APOC areas) having skin disease of the severest kind (e.g. hanging groin, severe chronic papillary onchodermatitis, or extensive lichenified onchodermatitis).

Given the larger geographical scope and the inclusion of a wider spectrum of sequelae in the GBD 2010 Study, the pre-control burden should have turned out higher than the estimate presented in **Chapter 5**. However, due to choices in the process of calculating the burden of all diseases and aggregating results globally, the estimated burden of onchocerciasis in 1990 actually turned out much lower (512 thousand DALYs lost globally; 441 thousand DALYs lost in regions later covered by APOC) than our estimates for 1995 (1.7 million DALYs lost in APOC regions). The most important cause for this discrepancy was that the burden of onchocercal skin disease was calculated using only disability weights for disfiguring skin dis-

ease "without itch or pain" (three severity levels: 0.013, 0.072, and 0.398); disability weights for disfiguring skin disease "with itch or pain" were not used (0.029, 0.187, and 0.562), effectively meaning that onchocercal itch was not considered. Moreover, the disability weight for the highest severity level of skin disease (0.398) was erroneously set to zero. Furthermore, excess mortality from blindness was not considered in the GBD 2010 Study, reducing the estimated global burden of onchocercal blindness in 1990 by 85 % (from about 500 thousand DALYs to about 80 thousand DALYs lost in APOC areas). A last minor cause for the discrepancy is that in the GBD 2010 Study, burden estimates for all diseases were shrunk somewhat to fit in so-called disease envelops (groups of diseases that cause the same symptoms) and to account for concurrent symptoms of different diseases.

In conclusion, we provide improved estimates of the pre-control burden of onchocerciasis, based on systematically collected data on pre-control infection levels and history of mass treatment. Our estimates highlight the importance of skin disease for the burden of onchocerciasis.

What has been the impact of ivermectin mass treatment, and what can be expected in the future?

In **Chapter 4** (Coffeng et al. 2013b) we report that between 1995 and 2010, ivermectin mass treatment has considerably reduced the prevalence of *O. volvulus* infection, onchocercal blindness, visual impairment, and troublesome itch. In **Chapter 5**, we estimated that ivermectin mass treatment has reduced the disease burden due to onchocericasis in APOC target areas from 23.1 DALYs per 1,000 persons to 8.6 DALYs per 1,000 persons, and will further reduce the disease burden to 3.7 DALYs per 1,000 persons by 2015. Cumulatively, ivermectin mass treatment was estimated to have averted 8.9 million DALYs between 1995 and 2010, and to further avert 10.1 million DALYs between 2011 and 2015 in APOC target areas. This health impact was estimated to cost about US$30 per DALY averted, which is comparable to the cost of other large scale control programs against tropical infectious diseases, and is highly cost-effective, when compared to the gross domestic product of beneficiary countries

(**Chapter 4**; Coffeng et al. 2013b).

In addition to the impact on the disease burden of onchocerciasis, we roughly estimated that between 1995 and 2010, ivermectin mass treatment has averted another 500 thousand DALYs related to off-target diseases such as soil-transmitted helminths, strongyloidiasis, ecto-parasitic infections, and lymphatic filariasis (**Chapter 6**). This estimate was based on the disease burden per capita of off-target diseases reported in the GBD 2010 Study (Murray et al. 2012), APOC records on number of people annually treated with ivermectin, and a review of literature that yielded rough estimates of the effects of ivermectin on off-target diseases. Compared to the impact of APOC on the disease burden of onchocerciasis, the additional health impact of ivermectin mass treatment on off-target diseases through 2010 is modest (5.5 %), though not negligible. In reality, the impact on off-target diseases may be even somewhat larger, as we did not consider the effects of ivermectin mass treatment on the intensity of infection and transmission of off-target diseases in populations not eligible for ivermectin treatment (children under five and pregnant women).

In light of APOC's paradigm shift from control to elimination (APOC 2010), we estimated the impact of increasing the frequency of ivermectin mass treatment on the prospects of elimination (**Chapter 7**). Based on ONCHOSIM simulations, we predicted that increasing mass treatment frequency will shorten program duration required to achieve elimination by 40 % (6-monthly treatment) or 60 % (3-monthly treatment). This reduction always comes at a cost of additional treatment rounds required to achieve elimination. We concluded that increasing mass treatment frequency from annual to 6-monthly is only attractive in settings where annual mass treatment is expected to take long to achieve elimination despite good coverage, i.e. hyperendemic areas where mass treatment started only recently. In low coverage settings, increasing coverage should have priority over increasing the frequency of mass treatment, as this is just as effective in terms of program duration required to achieve elimination, and more efficient in terms of the required number of mass treatment rounds. Increasing the frequency to 3-monthly seems to be entirely unattractive due to the highly increased number of mass

treatment rounds required to achieve elimination (compared to continuing annually or 6-monthly). Still, it may be necessary to switch to 3-monthly mass treatment in problematic areas where ivermectin mass treatment started only recently, if elimination is to be achieved by 2025.

In conclusion, APOC has had a considerable impact on population health in Africa through prevention of onchocercal eye and skin disease, and prematury mortality associated with blindness. In addition to that, APOC has had a modest, though non-negligible impact on the burden of off-target diseases. Furthermore, we provide considerations and recommendations for increasing mass treatment frequency, in light of elimination of African onchocerciasis. In the next section we discuss some methodological aspects and identify further research needs.

Critical appraisal of ONCHOSIM

All estimates of the impact of onchocerciasis control in Africa presented here were made by means of simulation studies using the microsimulation model ONCHOSIM (Plaisier et al. 1990; Habbema, van Oortmarssen, and Plaisier 1996). As discussed in **Chapter 4** (Coffeng et al. 2013b), the validity of model predictions relies on the quality of the model and its assumptions, and the quality of the input data. In previous studies, ONCHOSIM predictions could succesfully reproduce (trends in) infection levels observed in the field (Plaisier et al. 1991a,b, 1995). Still, there is a need to further develop ONCHOSIM and compare its predictions to field data, with the most important topics being ivermectin efficacy, transmission in hypoendemic areas, heterogeneity in individual exposure to fly bites, and migration of humans and flies.

Predicted effects of ivermectin mass treatment

To further validate our assumptions about drug efficacy (assumption set 1), we recently compared ONCHOSIM predictions to published longitudinal data from Senegal and Mali (Diawara et al. 2009) and found that model-predicted trends in infection levels (community microfilarial load and mf prevalence) during 14 to 16 years of mass

treatment were broadly consistent with the observed trends; some example comparisons for hyperendemic villages are presented in Figure 8.1. However, for some villages, observed infection levels seemed to decline slightly faster than the model predictions. One explanation for this is that ONCHOSIM may be too pessimistic regarding the permanent effects of ivermectin on adult worms (e.g. in terms of sterilizing or macrofilaricidal effects). Alternatively, the discrepancy could be explained by inaccurate or incomplete information about pre-control infection levels and/or history of mass treatment; however, this is difficult to confirm. Another explanation is that in the field, individual non-attendance to mass treatment may have been less systematic than assumed in ONCHOSIM, or may decrease over time. Systematic non-attendance to mass treatment (e.g. related to occupation or personal inclination to participate) may allow for infections to endure in human subpopulations, causing a slower decline of infection rates in the population during control. Last, ONCHOSIM may not adequately simulate transmission dynamics for low infection levels in the human population. Currently we only assume negative density-dependence at the level of mf-uptake by flies; however, there may be facilitation (positive density-dependence) in transmission at very low infection levels in the human population, as suggested for lymphatic filariasis (Subramanian et al. 2004). This would mean that once control has achieved very low levels of infection, transmission becomes relatively inefficient. Some potential mechanisms for facilitation are that nodules with more female worms are easier to find for male worms, and/or that the probability of succesful moulting of L1 larvae in flies increases with the number of ingested mf as in anopheline transmission of lymphatic filariasis (Southgate and Bryan 1992). Any or a combination of the aforementioned factors may explain why ONCHOSIM predictions for situations with long-term control seem to be somewhat pessimistic. Therefore, these factors merit further investigation and should be addressed in ONCHOSIM, where appropriate.

In **Chapter 7**, we re-evaluated our assumptions about ivermectin efficacy (assumption set 1), incorporating the latest evidence about the possible macrofilaricidal effects of ivermectin in ONCHOSIM (resulting in assumption set 2). Predictions based on

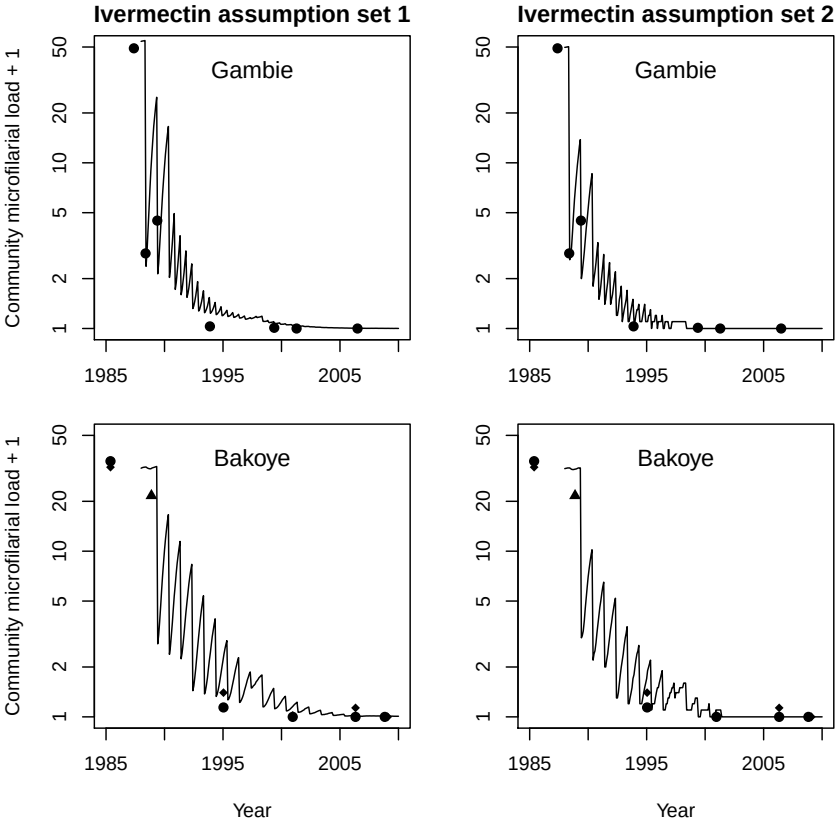

Figure 8.1: Comparison of ONCHOSIM-predicted trends in infection (graph lines) during 15 to 17 years of ivermectin mass treatment to previously published data (symbols) from one hyperendemic village in the River Gambie focus (annual and 6-monthly mass treatment) and three hyperendemic village in the River Bakoye focus (annual mass treatment only; Diawara et al. 2009). ONCHOSIM predictions were based on two alternative assumption sets for ivermectin efficacy (set 1 and 2) that consist of original and updated assumptions, respectively (for details, see **Chapter 7**). After about ten mass treatment rounds (1994–1995), the model predictions based on ivermectin assumption set 1 are somewhat pessimistic.

these updated assumptions could adequately reproduce trends in infection as observed in Senegal and Mali (Figure 8.1, panels on the right), and in Corriente Grande, Ecuador (unpublished), and fitted the data even slightly better than predictions based on the original assumptions (i.e. ONCHOSIM predictions were less pessimistic in terms of the effect of ivermectin on infection levels; Figure 8.1, panels on the left). In **Chapter 7**, we also concluded that the updated assumptions yielded slightly more optimistic predictions for the prospects of elimination under annual mass treatment (one year shorter program duration required for elimination). However, predictions for prospects of elimination under 6-monthly and 3-monthly mass treatment did not differ between the two assumption sets. This implies that if ivermectin is more efficacious than assumed in assumption set 1, we would expect a smaller benefit from increasing the frequency of mass treatment as annual mass treatment is already very effective.

Although the studies reviewed in **Chapter 7** provide convincing evidence of the existence of macrofilaricidal effects of ivermectin, none provide data detailed enough to precisely quantify the temporary and permanent effects of ivermectin on adult worms. Therefore, the questions remains whether macrofilaricidal effects of ivermectin (per treatment) are larger at higher treatment frequencies or after repeated treatments. If so, this would mean that we are currently underestimating the added benefit of high frequency mass treatment. Further investigation of such an effect would require adequately powered studies providing detailed data on the effects of ivermectin on adult worms. However, given ethical constraints regarding large scale nodulectomy, and the upscaling of ivermectin mass treatment, it is probably not feasible to gather a large enough sample of worms from treatment-naive humans. In due time, ONCHOSIM predictions should be compared to results from elimination programs that have switched to higher treatment frequencies.

Transmission of infection in hypoendemic areas

ONCHOSIM predicts that in hypoendemic areas (nodule prevalence in adult males $< 20\,\%$), an endemic equilibrium can not be sustained by local transmission only. A plausible assumption is that

hypoendemic areas are merely the results of infection spilling over from neighboring mesoendemic and hyperendemic areas via migrating infected flies and/or humans. This would be even more likely if there actually is facilitation (positive density dependence) in transmission at low levels of infection (see previous subsection on effects of ivermectin), which would make stable transmission in hypoendemic areas even more difficult. Still, it has been suggested that stable transmission is possible in hypoendemic areas (Katabarwa et al. 2010). Theoretically, this would be possible with very high inter-intervidual variation in exposure to fly bites (few infected individuals, but each with relatively high worm loads; Subramanian et al. 2004), and/or when there are additional mechanisms making transmission relatively efficient at low infection levels, e.g. negative density-dependent parasite establishment and/or mf survival due to host immunity (as in bovine onchocerciasis (Tchakouté et al. 2006) and lymphatic filariasis (Subramanian et al. 2004)), or density-dependent fly survival (Basáñez, Churcher, and Grillet 2009). Most likely, density-dependent fly survival is the easiest factor to investigate (and calibrate in the model), as fly survival can be directly observed. Density-dependent parasite establishment and mf survival are more difficult to prove as they can only be confirmed indirectly, based on a shift in the host age at which parasite loads peak during control (Woolhouse 1998; Subramanian et al. 2004). However, other potential causes for such a peak shift would have to be ruled out, such as excess mortality due to infection (Little et al. 2004a; Walker et al. 2012), which may be difficult. Nevertheless, given the existence of a hyperreactive form of onchocerciasis (marked by low mf loads, a specific immune response, and lichenified onchodermatitis), it is not unlikely that there are also less visible forms of host immunity against onchocerciasis that may significantly influence transmission. These mechanisms should be further investigated and implemented in ONCHOSIM, if applicable.

Heterogeneity in individual exposure to fly bites

There is still a need to better quantify heterogeneity in individual exposure to fly bites in ONCHOSIM (i.e. inter-individual variation in *relative* exposure to fly bites, where *relative* refers to the mean

biting rate in a population). This heterogeneity is an important factor in the elimination of onchocerciasis (**Chapter 7**; Winnen et al. 2002); situations with high heterogeneity in exposure to fly bites require longer program duration to achieve elimination. Most likely, heterogeneity is lower in high transmission settings, i.e. in villages close to fly breeding sites where flies are ubiquitous. Furthermore, patterns in variation may differ between forest and savanna areas, as in forest areas fly breeding sites may be more evenly spread due to presence of multiple small streams, rather than a single or a few large streams as in savanna areas. The association between mean infection levels and individual heterogeneity has been previously quantified, based on community level (Basáñez et al. 2002) and individual level data (Filipe et al. 2005). However, in both cases, quantification was performed assuming density-dependent mechanisms in both flies and humans (density-dependent parasite establishment). As ONCHOSIM currently only assumes density-dependence in the uptake of skin mf by flies, aforementioned estimates of variation in exposure can not be used in ONCHOSIM; they would result in too much variation in predicted skin snip counts, as such variation is not countered by density-dependent parasite establishment. Therefore, for the quantification of ONCHOSIM, heterogeneity in individual exposure should be investigated more directly by means of a statistical analysis of individual data on pre-control skin mf density from a set of villages with different mean pre-control infection levels (e.g. in a gamma-Poisson regression model). This analysis should relate heterogeneity in individual skin mf densities to mean skin mf levels per village. For villages outside the dataset, the amount of heterogeneity may be estimated from the mean infection level (if there is an association between the two). Results of these analyses could be translated to serve as input parameters for ONCHOSIM simulations by fitting simulation output to the expected distribution of skin snip counts (given some observed mean pre-control infection level).

Migration of humans and flies

Ideally, ONCHOSIM should account for migration of infected humans and flies, an important challenge for elimination of onchocerci-

asis (Dadzie, Neira, and Hopkins 2003). Currently, ONCHOSIM can only simulate onchocerciasis in a closed population, i.e. assuming no migration of (infected) flies or humans from or to neighbouring regions. Human migration is particularly important in settings of civil unrest, such as in the Democratic Republic of Congo and the border area between Sudan and South Sudan (Centers for Disease Control and Prevention (CDC) 1995). Furthermore, migration may be important at a more local level, for instance in case of seasonal migration of plantation workers.

In West Africa, migration patterns of *Simulium* flies have been well documented (Dadzie, Neira, and Hopkins 2003). In savanna areas, flies may travel up to 400 km on the wind. Migration patterns of forest *Simulium* species are less well documented; however, it is commonly known that forest *Simulium* species are relatively stationary, possibly due to the relative lack of large open spaces where flies can get picked up by the wind. Studies in West Africa suggest that transmission from savanna to forest areas and vice versa is limited by incompatibility of parasite-vector complexes, with the exception of *S. soubrense*, which can effectively transmit both savanna and forest parasite types (Dadzie, Neira, and Hopkins 2003). In light of elimination efforts, APOC is preparing studies to investigate fly migration patterns in Central Africa. These should shed more light on the importance of fly migration for transmission of onchocerciasis within forest areas and between forest and savanna areas. To better guide elimination efforts, accurate information on human and *Simulium* migration should also be incorporated in ONCHOSIM (e.g. simulation of a group of villages).

The future of onchocerciasis control in Africa

In the coming two decades, onchocerciasis control in Africa will be facing a number of changes and challenges. First of all, APOC has changed its objective from morbidity control to elimination of onchocerciasis by 2025 in 80 % of the countries covered by APOC (Onchocerciasis elimination workshop, March 4–8, 2013, Ouagadougou, Burkina Faso). APOC has developed a conceptual framework describing phases, tools, and benchmarks for assessing progress towards

elimination, deciding to stop mass treatment, monitoring and evaluation, and verifying elimination (APOC 2010). For evaluation of progress towards elimination, observations from the field will be compared to a set of standard ONCHOSIM predictions. To identify causes of gross discrepancies between observations and predictions, accurate information will be needed with regard to infection levels, the history of control, civil unrest, and/or presence of signification migration of infected humans or flies. After stopping mass treatment, the phase of monitoring and evaluation of transmission will require highly specific tests for detection of remaining or returning infections in settings of low intensity infection, such as fly pool screening (Katholi and Unnasch 2006; Gopal et al. 2012) and the DEC patch test (Ozoh et al. 2007). Aforementioned tests should also be included in ONCHOSIM, as this would allow test results to be interpreted in terms of the probability of elimination.

A second, major challenge for onchocerciasis control and elimination programs is *Loa loa* (African eye worm), which is endemic in considerable parts of the APOC region (Tekle et al. 2011; Zouré et al. 2011). Like onchocerciasis, loiasis is a filariasis and *L. Loa* mf are killed by ivermectin. Individuals with high *L. Loa* mf loads who are treated with ivermectin are at risk of severe, possibly fatal adverse effects such as cerebral oedema (Gardon et al. 1997; Awadzi 2003; Boussinesq 2006). In some areas where loiasis is endemic, fear of severe adverse effects has led to low mass treatment coverage. On top of this, in most of these areas, CDTI has been implemented relatively recently. As a consequence, these areas are lagging behind in progress towards elimination and may serve as sources of recrudescence of infection in surrounding areas where elimination has been established. Because high frequency ivermectin mass treatment is not a justifiable option to achieve elimination in such settings, alternative safe interventions are needed, such as vector control, test and treat strategies, interventions that safely reduce *L. Loa* loads, or alternative drug treatments against onchocerciasis, e.g. doxycyclin (Hoerauf 2008; Hoerauf et al. 2009; Specht et al. 2009; Wanji et al. 2009; Albers et al. 2012) or flubendazole (Mackenzie and Geary 2011). Currently, APOC is considering a test and treat strategy, which relies on the exclusion of high risk individuals from mass

treatment, based on a simple test for detection of high *L. Loa* loads. Again, all aforementioned interventions should ideally be modeled in ONCHOSIM, allowing their effects to be predicted in terms of prospects of elimination.

Third, there are concerns about *O. volvulus* worms developing resistance against ivermectin. For instance, there are reports of polymorphisms of the beta-tubulin gene in worms from treated populations (Eng and Prichard 2005; Bourguinat et al. 2006; Eng et al. 2006). Supposedly, these polymorphisms may enhance survival of worms and/or mf, at the cost of reduced fecundity of adult worms (Bourguinat et al. 2007). Furthermore, there are reports of individuals with abnormally high skin mf loads after ivermectin mass treatment (Awadzi et al. 2004a,b; Osei-Atweneboana et al. 2011). Several explanations have been proposed, such as that some female worms may be immune to the drug's fecundity-reducing effect (Osei-Atweneboana et al. 2007, 2011). Alternatively, these findings have been attributed to low treatment coverage (Burnham 2007; Cupp et al. 2007; Mackenzie 2007; Remme et al. 2007) and variation associated with the skin snipping technique (Mackenzie 2007; Churcher et al. 2009) and/or host genetics (Kudzi, Dodoo, and Mills 2010; Pion et al. 2011), rather than parasite resistance. It has also been noted that absolute mf counts may not be a good indicator of emerging resistance (Churcher and Basáñez 2009; Churcher et al. 2009). Rather, changes in patterns of mf skin repopulation are indicative of emerging resistance. Though the debate is ongoing, most experts agree that there is a need to keep monitoring for possible emergence of resistance. In case of resistance, drugs such as doxycyclin and flubendazol may have to be used for the further control and elimination of onchocerciasis.

Fourth, as APOC will come closer to achieving elimination of onchocerciasis, advovacy will become increasingly more important. Program costs will rise (costs associated with monitoring and evaluation), while program funders may have to deal with economic depression. Also, the perceived importance of elimination may decline as the issue of onchocerciasis will become less and less visible. Therefore, elimination of African onchocerciasis can only be achieved with intensified support from all stakeholders and funding parties,

and through continued close collaboration between scientists and policy makers. In light of the latter, ONCHOSIM predictions can provide support for advocacy and policy making.

Following the success of APOC's community-directed strategy, in several regions interventions against other diseases have been integrated with CDTI against onchocerciasis, such as health education for schistosomiasis and lymphatic filariasis, distribution of insecticide-treated bednets against malaria and lymphatic filariasis, and vitamin A suppletion (Hopkins et al. 2008). Integration of control programs could lead to lower resource requirements due to common features of control interventions against different diseases. Integrated control of human helminthiasis has the attention of many (Molyneux 2006; Hotez et al. 2008), and guidelines for what drugs should be used in different areas have already been formulated (WHO 2006). Large-scale control programs against helminths have already been initiated in parts of the world (Kabatereine et al. 2006; Padmasiri et al. 2006; Montresor et al. 2008; Addiss and The Global Alliance to Eliminate Lymphatic Filariasis 2010), though not yet on the entire African continent. In light of this development, APOC may evolve into a larger public health program against a wide range of diseases, or at least serve as a successful example for future control programs. Whether integration will eventually take place will largely depend on successful collaboration between stakeholders and the different donor parties, and political support from within beneficiary countries.

Conclusions and recommendations

Conclusions

1. Onchocerciasis control has had a considerable impact on population health in Africa, preventing disability due to eye and skin disease, and premature mortality associated with blindness.

2. Mass treatment with ivermectin is a highly cost-effective public health intervention against onchocerciasis.

3. Onchocercal skin disease and the associated itch are important

contributors to the disease burden of onchocerciasis, but are not yet fully captured in existing estimates of the burden of onchocerciasis.

4. In low coverage settings, increasing mass treatment coverage is just as effective for achieving elimination as increasing mass treatment frequency, though costs fewer mass treatment rounds.

5. The health impact of APOC has been made possible through contributions by many different (inter)national and local stakeholders and funding parties, and close collaboration between policy makers and scientists.

6. Central registration of data on pre-control infection levels and on the history of ivermectin mass treatment have provided pivotal input for the quantification of the health impact of APOC.

Recommendations for policy

1. Elimination of African onchocerciasis can only be achieved with intensified support from all stakeholders and funding parties, and through continued close collaboration between scientists and policy makers.

2. Increasing mass treatment frequency should only be considered in areas where annual treatment is not expected to achieve elimination by 2025 despite good coverage.

3. National control programs should maintain high program coverage and ensure accuracy of data on population coverage of mass treatment and human migration.

Recommendations for scientific research

1. In light of elimination of African onchocerciasis, there is a need for more information on migration of humans and *Simulium* flies in Central Africa.

2. To accurately predict program duration required for elimination of onchocerciasis, there is a need to better quantify systematic non-compliance to mass treatment and inter-individual variation in exposure to infection.

3. It should be clarified whether local transmission is taking place in hypoendemic areas, and if so, how this is possible.

4. More sensitive tests for the presence of *O. volvulus* infection are needed to monitor progress towards elimination and verify interruption of transmission.

5. Further development of alternative drugs such as doxycyclin and flubendazole can help to deal with loiasis co-endemicity and possible emergence of worm resistance against ivermectin.

6. ONCHOSIM should be further developed, incorporating information on disfiguring skin disease, transmission dynamics in settings of low intensity infection, migration of humans and flies, and new diagnostic techniques and intervention strategies.

Appendix A
Supplement to Chapter 2

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Model description

The current study considers spatially clustered, bivariate binomially distributed data. For analysis of spatial data, there are geostatistical techniques that take account of the spatial correlation. These techniques require knowledge of the geographical coordinates of the data points, which were not fully available in our case. Instead, we used an ordinary hierarchical approach to model the data to account for spatial correlation.

There are several popular alternatives for modeling bivariate binomially distributed data. Multivariate probit regression models have been proposed. These models are convenient in terms of computational requirements because they only quantify the correlation between observations, leaving variance at the lowest level of the data unidentified (but accounted for; O'Brien and Dunson 2004). Depending on the researcher's objective, this can be considered an advantage (computationally less demanding) or a drawback (part of the model remains unidentified). Another drawback is that the interpretation of probit models may be less intuitive to some, if not many researchers. As a concession to these arguments, a reparameterization of the multivariate logistic regression model has been proposed, which like the probit model leaves the variance at the lowest level unidentified (O'Brien and Dunson 2004; Ovaskainen, Hottola, and Siitonen 2010). However, this reparameterized logistic model requires a customized sampling algorithm for efficient Markov chain Monte Carlo sampling. In our case, we chose for intuitive interpretation, quantification of all variances, and the use of the freely available and widely implemented Gibbs sampling algorithm, leading to the choice of generalizing the familiar logistic model as described below.

The multivariate model used in this study is an extension of the hierarchical logistic regression model

$$\text{logit}(\pi_{ij}(y_{ij}|X_{ij}, \beta, n_{ij})) = X_{ij}^T\beta + \epsilon_{ij} + \epsilon_j \qquad \text{(A.1)}$$

where π_{ij} is the probability of finding y cases of some binomially distributed outcome in n individuals from the i-th unit in the j-th cluster, conditional on a set of observed covariates X_{ij} and a set of model parameters β. The error terms ϵ_{ij} and ϵ_j represent the

variation within and between the j clusters of observation, respectively. We extended this model to simultaneously predict m binary outcomes, leading to

$$\text{logit}(\pi_{ij,m}(y_{ij,m}|X_{ij}, \beta_m, n_{ij,m})) = X_{ij}^T \beta_m + \epsilon_{ij} + \epsilon_j \qquad \text{(A.2)}$$

where $\pi_{ij,m}$ is the probability of observing y cases of the m-th outcome ($m = 1$: presence of microfilariae in the skin; $m = 2$: presence of nodules in adult males) among n_m observed individuals from the i-th unit (village) in the j-th cluster (geographical area). Here, the error terms ϵ_{ij} and ϵ_j each consist of m components representing the variation in log odds of each of the m outcomes within and between the j clusters of observations. For each set of m observations, there is a set of observed covariates X_{ij} (bioclime), and for each of the m predicted binary outcomes we have a set model parameters β_m. In our case, the intercepts $\beta_{0,m=1}$ and $\beta_{0,m=2}$ represent the mean log odds of presence of mf and nodule in the reference group, respectively. The parameters $\beta_{1,m=1}$ and $\beta_{1,m=2}$ represent the log odds ratio of observing presence of microfilariae in the skin and subcutaneous onchocercal nodules in a certain bioclime, respectively, relative to a reference bioclime (multiple sets of such parameter can be added to stratify the analysis by multiple bioclimes and/or other characteristics). Correlation between onchocercal nodule and mf prevalence was modeled by assuming multivariate normal (MVN) distributions for the error terms:

$$\epsilon_{ij} \sim \text{MVN}(\mu_{\epsilon_{ij}}, \Sigma_{\epsilon_{ij}}) \qquad \text{(A.3)}$$

$$\epsilon_j \sim \text{MVN}(\mu_{\epsilon_j}, \Sigma_{\epsilon_j}) \qquad \text{(A.4)}$$

with $\mu_{\epsilon_{ij}} = \mu_{\epsilon_j} = (0, 0)$. Here, $\Sigma_{\epsilon_{ij}}$ and Σ_{ϵ_j} are variance-covariance matrices with dimensions $m \times m$, containing along the diagonal the marginal variances of the log odds of presence of nodules and mf within ($\sigma^2_{ij,m=1}$ and $\sigma^2_{ij,m=2}$) and between ($\sigma^2_{j,m=1}$ and $\sigma^2_{j,m=2}$) the j clusters of observations. The off-diagonal positions of $\Sigma_{\epsilon_{ij}}$ and Σ_{ϵ_j} hold the covariances $\sigma_{ij,m=1;m=2}$ and $\sigma_{j,m=1;m=2}$ of the log odds of presence of nodules and mf within and between the j clusters, respectively. The correlation between log odds of presence of nodules and mf at village-level ρ_{ij} was derived as follows:

$$\rho_{ij} = \frac{\sigma_{ij,m=1;m=2}}{\sigma_{ij,m=1} \times \sigma_{ij,m=2}} \qquad \text{(A.5)}$$

Correlation ρ_j was derived in a similar fashion, and can be interpreted in two ways; 1) together with variances $\sigma^2_{j,m=1}$ and $\sigma^2_{j,m=2}$, ρ_j represents how the association between onchocercal nodule and mf prevalences varies between geographical regions due to e.g. environmental factors and surveys methods (analogous to linear regression models with a random intercept); 2) ρ_j is the correlation between the mean log odds of presence of nodules and mf in a geographical area (as defined for the data in this study).

Parameter estimation

Model parameters were estimated assuming non-informative prior distributions. For fixed effects parameters β_m, we assumed independent normal prior distributions $\mathrm{N}(0, 1000)$. The village-level variance-covariance matrix $\Sigma_{\epsilon_{ij}}$ was estimated assuming a scaled Wishart prior distribution $\mathrm{Wish}(R, k)$ for its inverse $\Sigma^{-1}_{\epsilon_{ij}}$, where R is the $m \times m$ identity matrix I_m, and k is the number of degrees of freedom (set to 3, effectively assuming uniform prior information on ρ_{ij}). To maximize the speed of model convergence, the variance-covariance matrix Σ_{ϵ_j} for variation between geographical areas was hierarchically centered around fixed effects β_m, and was estimated assuming independent uniform prior distributions for the correlation ($\rho_j \sim \mathrm{U}(-1, 1)$), and standard deviations ($\sigma_{j,m} \sim \mathrm{U}(0, 10)$ or $\sigma_{j,m} \sim \mathrm{U}(0, 100)$), in line with previous recommendations for estimating hyperparameters (Gelman 2006). The prior distribution for minimum sensitivity of nodule palpation (at low endemicity levels) was defined as being uniform between 60 % and 100 %. The prior distribution for specificity of nodule palpation was defined as being uniform between 98 % and 100 %.

Model parameters were estimated using four Markov chains with each 400,000 Monte Carlo simulations. For each chain, the first 200,000 of the saved simulations were considered as burn-in simulations and discarded. Such a number of simulations was necessary as the Gibbs sampler explored the joint posterior distribution of parameters slowly, indicated by high autocorrelation of Monte Carlo samples. To save storage space, only every 20^{th} Monte Carlo sample was stored, effectively reducing autocorrelation (Figure A.1). The

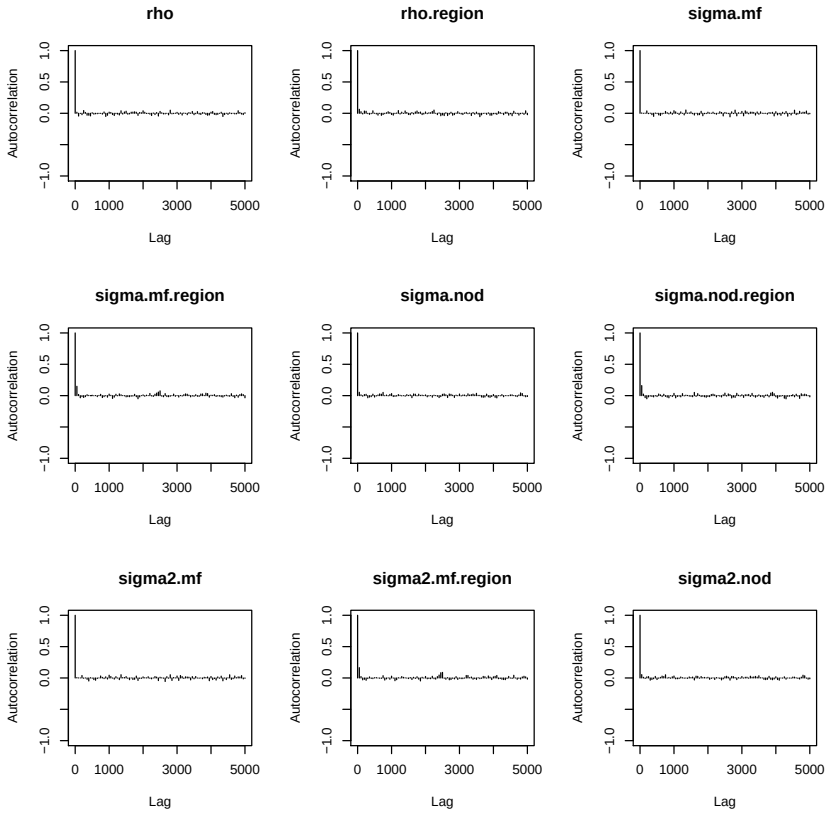

Figure A.1: Autocorrelation plots of Monte Carlo samples for nine parameters. In this study, autocorrelation was initially high for some parameters, indicating that the sampling algorithm was slow in exploring the posterior distribution of these parameters. Autocorrelation was reduced by storing only every 20^{th} Monte Carlo sample and running 200,000 iterations (after discarding an initial 200,000 iterations for burn-in), for which the results are shown here. After this, autocorrelation of Monte Carlo samples was similarly low for all parameters and Markov chains.

effective amount of simulations per parameter was 40,000 (sum of four Markov chains). The point estimate for each parameter and prediction were taken to be the median of the 40,000 simulations. Ninety five percent Bayesian credible intervals were calculated as the 2.5^{th} and 97.5^{th} percentiles of the simulations.

Model convergence was assessed by checking whether the four Markov chains converged to the same posterior distribution for each parameter, based on Gelman and Rubin's convergence diagnostic, the potential scale reduction factor (which should be below 1.1; i.e. a posterior credible interval of a parameter estimate should not become more than 10 % narrower if more Monte Carlo samples were drawn) (Gelman and Rubin 1992). Because this diagnostic test requires that starting values for each parameter in each Markov Chain are over-dispersed with respect to the true posterior distribution of a parameter, we assigned heavily over-dispersed initial values to each of the model parameters in each chain (e.g. the initial values 1, 10, 50, and 100 for a parameter with an uninformative normal distribution as prior, one value for each Markov chain). In our simulations, the potential scale reduction factor was at or below 1.001 for all parameters. Furthermore, we checked that all Markov chains arrived in the joint posterior distribution of parameter values, as determined by means of Geweke's test, which compares the distribution of the first 10 % and last 50 % of the Monte Carlo samples within a chain (Geweke 1991). We also checked that Monte Carlo errors were small, relative to the point estimate of each parameter (difference of at least factor 100–1,000).

Model application

Given estimates of β_m, $\Sigma_{\epsilon_{ij}}$, and Σ_{ϵ_j}, we estimated the conditional distribution of mf prevalence $\pi^*_{ij,m=1}|\pi^*_{ij,m=2}$ in a hypothetical village i from an unspecified region j outside the dataset, given an estimate of the 'true' onchocercal nodule prevalence in adult males, corrected for misclassification of nodules, in the same hypothetical village (assuming this is exactly known). Given that we are working with multivariate normal distributions, the conditional distribution of $\pi^*_{ij,m=1}|\pi^*_{ij,m=2}$ can be described as:

$$\text{logit}(\pi^*_{ij,m=1}|\pi^*_{ij,m=2}) \sim \text{N}\big(\mu^*_{ij,m=1}, (1-\rho^2_{ij})\sigma^2_{ij,m=1}\big) \qquad \text{(A.6)}$$

where

$$\mu^*_{ij,m=1} = X^T_{ij}\beta^*_{j,m=1} + \frac{\sigma_{ij,m=1}}{\sigma_{ij,m=2}}\rho_{ij}\big(\text{logit}(\pi^*_{ij,m=2}) - X^T_{ij}\beta_{m=2}\big)$$
$$\beta^*_{j,m=1} \sim \text{N}\big(\beta_{m=1}, (1-\rho^2_j)\sigma^2_{j,m=1}\big)$$

To include uncertainty about nodule prevalence $\pi^*_{ij,m=2}$ in the prediction of mf prevalence $\pi^*_{ij,m=1}$, we simulated values from the estimated distribution of $\text{logit}(\pi^*_{ij,m=2})$, and fed these into the distribution for $\text{logit}(\pi^*_{ij,m=1}|\pi^*_{ij,m=2})$, from which values for $\pi^*_{ij,m=1}$ were then simulated. As this was done while simultaneously estimating the values of model parameters by means of Markov Chain Monte Carlo sampling, all uncertainty in the model parameter estimates was carried through to the final predictions for mf prevalence in hypothetical villages.

It should be noted that the procedure described above produces predictions pertaining to individual villages only, and therefore will produce predictions containing a great deal of uncertainty. The amount of uncertainty would be substantially lower if predictions were made based on larger samples of adult males, or when made for the mean prevalence of infection in a group of villages. However, a prediction for a mean prevalence would ignore possible heterogeneity in infection prevalences between villages, which may lead to overly optimistic estimates when e.g. when assessing prospects of elimination (the most highly endemic village will determine the required duration of an intervention, not the mean prevalence in a region). Nevertheless, if such predictions are made (e.g. for a group of villages with known similar levels of infection), or concerning many villages (theoretically an infinite number of villages), the mean mf prevalence is described by

$$X^T_{ij}\beta^*_{m=1} + \frac{\sigma_{ij,m=1}}{\sigma_{ij,m=2}}\rho_{ij}\big(\text{logit}(\pi^*_{ij,m=2}) - X^T_{ij}\beta_{m=2}\big) \qquad \text{(A.7)}$$

where $\pi^*_{ij,m=2}$ is the mean nodule prevalence in the group of villages (including uncertainty related to overall sample size). However, usually the number of sampled villages is not very high ($< 1{,}000$, meaning that the denominator of the standard error of the mean is < 30, approximately the square root of 1,000), and one should therefore simulate the mf prevalence separately for every village, sampling

village-level error independently for every village, and sampling the region-level error simultaneously for all villages. Then, for every set of many repeated simulations (i.e. a set consisting of one simulation for each village), the investigator can calculate the mean or any other summary statistic of the level of infection in the group of villages (e.g. range or variance), arriving at a distribution for the estimated mean or another summary statistic for mf prevalence in a group of villages.

Model specification in JAGS

```
for (i in 1:N) {
   # Likelihood of nodule data
   k.nod[i] ~ dbin(sens.nod.p[i] * p.nod[i] +
      (1-spec.nod)*(1-p.nod[i]), n.nod[i])
   sens.nod.p[i] <- sens.nod + (1-sens.nod)*p.nod[i]
   logit(p.nod[i]) <- B0[region[i],1] + e.vill[i,1]

   # Likelihood of mf data
   k.mf[i] ~ dbin(p.mf[i],n.mf[i])
   logit(p.mf[i]) <- B0[region[i],2] + e.vill[i,2]

   # Correlation of nodule and mf data with regions
   e.vill[i,1] <- e.vill.raw[i,1] * xi.nod
   e.vill[i,2] <- e.vill.raw[i,2] * xi.mf
   e.vill.raw[i,1:2] ~ dmnorm(Mu,Sigma2.inv.raw)
}

# Priors for fixed effects
sens.nod ~ dunif( [some value] ,1.0)
   # [some value] = 0.6, 0.8, or 1.0 (final model)
spec.nod ~ dunif(0.98 ,1)
b0.nod ~ dnorm(0,0.001)
b0.mf ~ dnorm(0,0.001)
mbam.nod ~ dnorm(0,0.001)
mbam.mf ~ dnorm(0,0.001)
```

```
# Uniform prior for correlation and marginal standard
# deviations of hierarchically centered random region
# effects
for (j in 1:7) {
   B0[j,1:2] ~ dmnorm(Mu.region[j,1:2],Sigma2.region.inv)
   Mu.region[j,1] <- b0.nod + mbam.nod*equals(j,2)
   Mu.region[j,2] <- b0.mf + mbam.mf*equals(j,2)
}
Sigma2.region.inv <- inverse(Sigma2.region)
Sigma2.region[1,1] <- sigma2.nod.region
Sigma2.region[2,2] <- sigma2.mf.region
Sigma2.region[1,2] <- covar.nod.mf.region
Sigma2.region[2,1] <- covar.nod.mf.region
covar.nod.mf.region <- rho.region * sigma.nod.region *
   sigma.mf.region
sigma2.nod.region <- pow(sigma.nod.region,2)
sigma2.mf.region <- pow(sigma.mf.region,2)
sigma.nod.region ~ dunif(0,10)
sigma.mf.region ~ dunif(0,10)
rho.region ~ dunif(-1,1)

# Scaled inverse Wishart prior for random village effects
Sigma2.inv.raw ~ dwish(R,scale)
xi.nod ~ dunif(0,100)
xi.mf ~ dunif(0,100)
Sigma2.raw <- inverse(Sigma2.inv.raw)
sigma.nod <- pow(Sigma2.raw[1,1],0.5) * xi.nod
sigma.mf <- pow(Sigma2.raw[2,2],0.5) * xi.mf
rho <- Sigma2.raw[1,2]/sqrt(Sigma2.raw[1,1] *
   Sigma2.raw[2,2])
Sigma2[1,1] <- pow(sigma.nod,2)
Sigma2[1,2] <- rho * sigma.nod * sigma.mf
Sigma2[2,1] <- Sigma2[1,2]
Sigma2[2,2] <- pow(sigma.mf,2)

# Predictions for REMO samples
sigma2.mf.REMO <- (1 - rho^2) * pow(sigma.mf,2)
```

```
sigma2.mf.REMO.region <- (1 - rho.region^2) *
   sigma2.mf.region
tau.mf.REMO <- pow(sigma2.mf.REMO,-1)
tau.mf.REMO.region <- pow(sigma2.mf.REMO.region,-1)

for (k in 1:N.REMO) {
   # Hypothetical REMO village: nodule prevalence
   k.nod.REMO[k] ~ dbin(sens.nod.p.REMO[k] *
      p.nod.REMO[k] + (1-spec.nod) *
      (1-p.nod.REMO[k]),n.nod.REMO[k])
   sens.nod.p.REMO[k] <- sens.nod +
      (1-sens.nod) * p.nod.REMO[k]
   logit(p.nod.REMO[k]) <- b.nod.REMO[k]
   b.nod.REMO[k] ~ dnorm(0,0.001)

   # Hypothetical REMO village: mf prevalence (non-mosaic)
   logit(p.mf.REMO.vill[k]) <- b.mf.REMO.vill[k]
   b.mf.REMO.vill[k] ~
      dnorm(b0.mf.REMO.region[k],tau.mf.REMO)
   b0.mf.REMO.region[k] <- b0.mf.REMO.intercept[k] +
      (sigma.mf/sigma.nod) * rho * (b.nod.REMO[k] - b0.nod)
   b0.mf.REMO.intercept[k] ~
      dnorm(b0.mf,tau.mf.REMO.region)

   # Hypothetical REMO village: mf prevalence (mosaic)
   logit(p.mf.REMO.vill.mosaic[k]) <-
      b.mf.REMO.mosaic.vill[k]
   b.mf.REMO.mosaic.vill[k] ~
      dnorm(b0.mf.REMO.mosaic.region[k],tau.mf.REMO)
   b0.mf.REMO.mosaic.region[k] <-
      b0.mf.REMO.mosaic.intercept[k] +
      (sigma.mf/sigma.nod) * rho * (b.nod.REMO[k] -
      (b0.nod + mbam.nod))
   b0.mf.REMO.mosaic.intercept[k] ~
      dnorm((b0.mf + mbam.mf),tau.mf.REMO.region)
}
```

Appendix B

Supplement to Chapter 4

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Estimating the population at risk

was available per calendar year from APOC's mass treatment database. The population estimates in this database are based on annual village census figures as reported by individuals responsible for the distribution of ivermectin in the community, aggregated to the project level.

In most projects, mass treatment was implemented over the years, starting in some villages and expanding geographically over the years. Also, over the course of time, some projects were expanded to cover larger areas, based on updated estimates of the geographical distribution of infection. Because for some projects, the mass treatment data only holds population estimates for areas where mass treatment was actually implemented, we regarded the year with the largest estimate (standardized to 2010, based on national population growth rates as reported by the United Nations World Population Prospects, published 11 May 2010, accessed 24 October 2011) as the reference year with the best estimate of the population at risk for infection. We then estimated the 'true' population at risk for all other years, based on national growth rates. Population sizes for the period 2011–2015 were extrapolated from the population sizes for 2010, assuming that the growth rates for 2011–2015 are equal to that of 2010.

Estimating the history of mass treatment with ivermectin in APOC

Information on the history of mass treatment with ivermectin was obtained from APOC's mass treatment database, which contains information by project and year about the number of people treated and the population size. In section S1, we already explained how we dealt with uncertainty in the data to estimate the total population of projects by year. Data on the number of persons treated were thought to be more robust, as these were reported by individuals responsible for distribution of ivermectin who are trained to observe people when they take ivermectin. Also, ivermectin distributors are retrained every year for at least three consecutive years, which should

improve the robustness of the reported data. The therapeutic coverage, here defined as the fraction of the population that was treated with ivermectin, by year and project, was estimated by dividing the number of reported persons treated by the size of the target population (size based on the corrected estimate, described in S1). The calculated therapeutic coverage represents the average coverage in a project population in each year. We did not mimic between-village variation in coverage, which is perhaps most extreme in the phase of scaling up: in some projects, treatment started in a subpopulation with high coverage, while the other part of the population did not yet receive mass treatment (zero coverage). By taking the average, we may have been somewhat pessimistic about the impact of APOC, as low coverage in a large population is less effective than high coverage in a small population because of transmission effects. This may have been especially the case for situations where mass treatment started in the most highly endemic areas of a project.

Estimating the pre-control level of infection

Because the effect of mass treatment with ivermectin depends on the pre-control level of infection in a population (aside from therapeutic coverage), the health impact of APOC was estimated for strata of population exposed to different pre-control levels of infection, a proxy for intensity of transmission. To do this, we first estimated the geographical distribution of pre-control levels of infection and divided project populations in endemicity categories so that we could model trends in infection and morbidity accordingly. For this exercise we defined four categories of pre-control nodule prevalence: non-endemic (nodule prevalence in adult males $< 1\,\%$), hypoendemic ($\geq 1\,\%$ and $< 20\,\%$), mesoendemic ($\geq 20\,\%$ and $< 40\,\%$), and hyperendemic ($\geq 40\,\%$). The geographical distribution of infection in each project was expressed as the fraction of the population living in each endemicity category (Table 1 in main manuscript). We assumed that these fractions (representing geographical areas) were stable during the period for which calculations were done (1995 to 2015). Next, for each endemicity category, the mean pre-control prevalence of infection was determined, serving as a starting point for ONCHOSIM

simulations.

Categorization of project populations in endemicity categories

The distribution of infection in a project was estimated from the REMO database (Rapid Epidemiological Mapping of Onchocerciasis; Ngoumou and Walsh 1993; Noma et al. 2002). These data were assumed to be representative for the geographical area covered by APOC, in terms of population size and level of infection. The REMO data have been gathered according to a strict protocol: surveys were started in a selection of villages perceived to be at high risk for onchocerciasis transmission (e.g. close to a major river in an area where blackflies are known to be present). In each selected village, a sample of 30 to 50 adult males (age 20 years and older) was examined for onchocercal nodules (henceforth referred to as nodule prevalence). For any village that proves at least mesoendemic (nodule prevalence $\geq 20\,\%$), a secondary village at least 10 km away was also surveyed. The cut-off nodule prevalence of $\geq 20\,\%$ corresponds to an mf prevalence of $\geq 40\,\%$ and was used as an indication of considerable risk for onchocercal blindness in a community (Ngoumou and Walsh 1993; Noma et al. 2002).

Because the REMO data are based on samples of 30 to 50 individuals, there is a good chance that in low-endemic villages zero individuals with nodules are observed, and that in highly endemic villages all examined individuals have nodules (whereas the 'true' prevalence is not $0\,\%$ or $100\,\%$). In other words, the sampling error at the village level introduced additional variation in observed geographic distribution of nodule prevalences. Therefore, the variation of the observed distribution of nodule prevalences overestimates the true geographic variation in nodule prevalences. Consequently, when using the frequency distribution of nodule prevalences within a project as a measure of the geographical distribution of infection, the fraction of the population in low-endemic and highly endemic areas is overestimated. This error can be circumvented by taking account of the sampling error at the village level.

We assumed that in the REMO data, the reported number of adult males with nodules in each village (k) is a sample from a

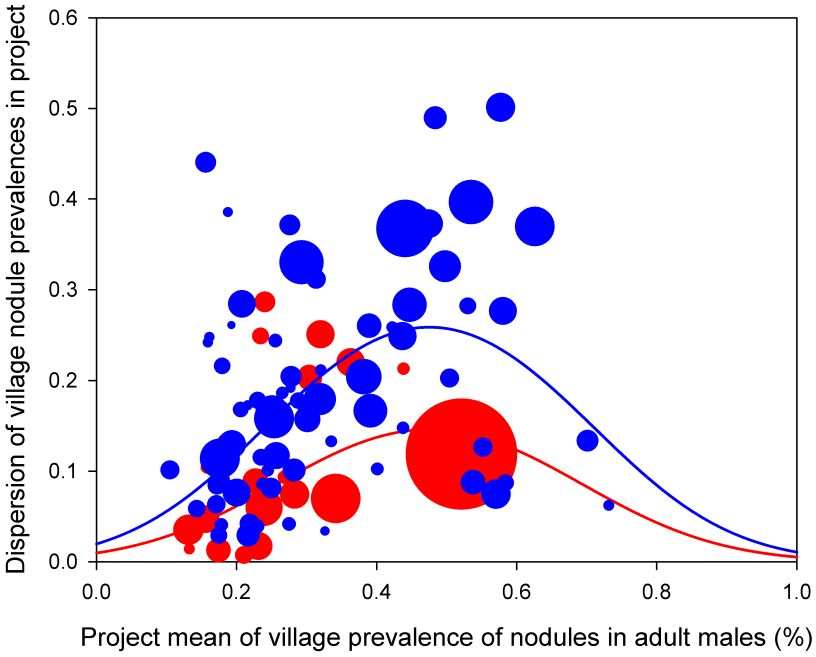

Figure B.1: Nodule prevalence in adult males: mean and dispersion per project and onchocerciasis type (blue represents forest/mixed areas; red represents savanna areas), as estimated from the database for Rapid Epidemiological Mapping of Onchocerciasis. Each data point represents a project; the size of each data point reflects the number of villages that was sampled in the project. The regression lines are based on a linear regression model that predicts the logit dispersion from the mean nodule prevalence in a project.

binomial distribution $\text{Bin}(n, p)$ with n equal to the number of observations and p representing the nodule prevalence among adult males. To circumvent the error described above, we assumed that for any given village p is unknown (i.e. p is not necessarily equal to k divided by n), and that the range of unknown nodule prevalences p within a project area follows a beta distribution $\text{Beta}(\alpha, \beta)$. This beta distribution then represents the 'true' but unobserved distribution of nodule prevalence in a project, and can be used to determine the fraction of the population in each endemicity category. For each project, we estimated the shape parameters α and β

of the beta distribution with a beta-binomial regression model in R+ (version 2.13.2, Vienna, Austria, 2011), using a maximum-likelihood approach (package VGAM) (Yee and Wild 1996). When no sample size n was available for a village in the REMO data, we assumed n equal to the median sample size of the other villages in the project area (usually ~ 30, only in Nigeria usually 50). If the sample sizes were unknown for all villages in a project (four projects in Uganda), a sample size of 30 was assumed, as specified in the REMO protocol (Ngoumou and Walsh 1993; Noma et al. 2002).

For each project we examined the dispersion of nodule prevalence within the project (a measure of heterogeneity, defined as $1/(1+\alpha+\beta)$). As may be expected, the dispersion of nodule prevalence was higher in forest areas (Figure B.1), probably because transmitting blackflies are restricted in their movement by dense forest, resulting in focally high prevalences of infection. Furthermore, dispersion of infection was associated with the mean prevalence of infection in the project ($\alpha/(\alpha+\beta)$); dispersion was highest for levels of infection around 50 % and was mostly lower for any other levels of infection (Figure B.1). Therefore, we standardized the dispersion of nodule prevalences over the whole APOC area by defining dispersion as a function of the mean nodule prevalence in a project. We used a linear regression model to predict the logit of the estimated dispersion within a project from the mean nodule prevalences in a project (Figure B.1). We included both a linear and a square term for nodule prevalence, assuming that the dispersion would be lowest at very high and very low mean prevalences. This assumption was robust, as final estimates of the health impact were very similar when based on the means and dispersions of infection levels, estimated without the constraint of a quadratic association between the two. We also included a linear term for type of onchocerciasis, allowing for differences in geographical distribution of infection in savanna and forest areas. The linear regression parameters were estimated in R+ (package *glm*), while weighting the data for the number of villages sampled per project (weight equal to square root of number of villages sampled in each project). Using this linear regression model, we re-estimated the dispersion of nodule prevalence in each project and calculated the final shape parameters of the beta distributions

of nodule prevalence.

Finally, for each project we calculated the fraction of the populations in each of the previously mentioned endemicity categories, based on the cumulative beta distribution of nodule prevalence in adult males.

Mean prevalence of infection per endemicity category

As explained above, we determined the mean pre-control nodule prevalence in each endemicity category to serve as a starting point for modeling trends in infection. To minimize variation due to the fact that for some projects relatively few villages were sampled, the mean pre-control nodule prevalence in each endemicity category was determined over the whole of APOC. This was done by taking 100,000 samples from the beta distribution of nodule prevalence for each project and dividing them in the aforementioned endemicity categories. Next, we calculated the overall mean nodule prevalence for each category over the whole of APOC, weighted for the size of the population in each project.

The mean nodule prevalence among adult males in mesoendemic areas was estimated at 29 %; for hyperendemic areas, it was estimated at 61 %. Because no simulations were performed for hypoendemic and non-endemic areas, there was no need to estimate the mean prevalence of infection for these categories.

Modeling trends in infection and morbidity in ONCHOSIM

Trends in prevalence of infection, blindness, visual impairment and mortality were simulated with the ONCHOSIM model (Plaisier et al. 1990, 1997). This model can simulate transmission of O. volvulus and development of morbidity in a community, while accounting for the effect of interventions such as mass treatment with ivermectin or vector control. For hypoendemic areas, ONCHOSIM predicts that transmission of infection is unsustainable without migration of infected flies and/or humans. Because information on migration was lacking, no simulations were performed for hypoendemic areas.

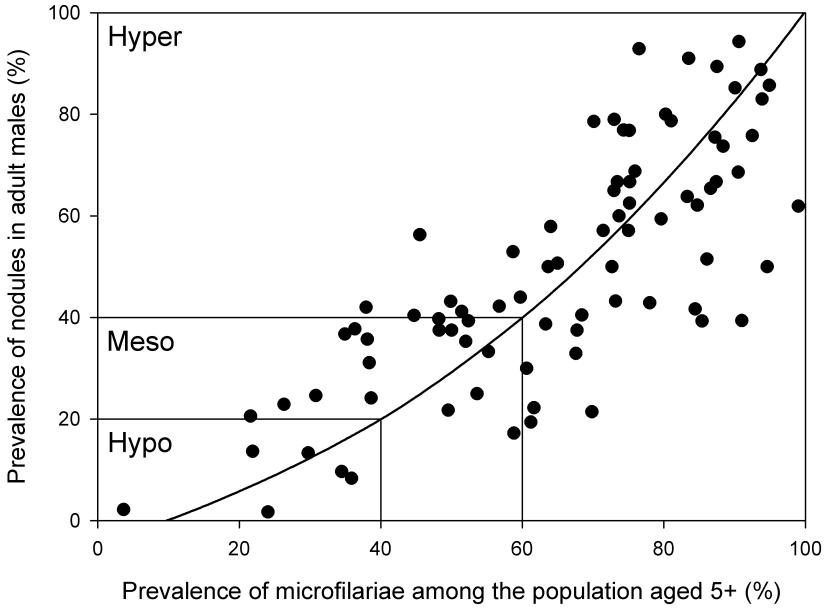

Figure B.2: The relationship between the prevalence of nodules in adult males and the prevalence of mf among the total population aged 5 years and older. The horizontal and vertical lines indicate the threshold values for the hypoendemic, mesoendemic and hyperendemic categories. Reproduced from a previous publication by Remme (2004).

Instead, we assumed that the prevalence of infection and morbidity in hypoendemic areas was 1/3 of that in mesoendemic areas, both pre-control and during control. For non-endemic areas, we assumed that prevalence of infection and morbidity was always zero.

Calibration of ONCHOSIM parameters for transmission

ONCHOSIM was calibrated to reproduce the pre-control levels of infection in each endemicity category, as estimated from the REMO data (S3.2). However, the REMO data are based on nodule prevalence in adult males, whereas ONCHOSIM provides output on preva-

Table B.1: Transmission parameters used for the simulation of mesoendemic and hyperendemic areas of APOC.

	Mesoendemic areas	Hyperendemic areas
Exposure heterogeneity[b]	3.865	4.283
Monthly biting rate[b]		
January	828	1,095
February	729	964
March	465	615
April	595	787
May	601	795
June	524	693
July	815	1,078
August	1,057	1,398
September	933	1,234
October	1,020	1,349
November	1,163	1,538
December	834	1,103

[a] Value of scale and shape parameters of a gamma distribution with mean 1, which models individual heterogeneity in exposure to infection. In other words, the average (expected) number of fly bites for a person of a certain sex and age is multiplied with an individually fixed index, which has been drawn from the aforementioned gamma distribution.

[b] Average number of fly bites per adult male person per month. These figures are proportional to biting rates observed in Asubende, Ghana, assuming that these seasonal patterns in biting rates are representative for other sites as well.

lence and load of microfilariae in the skin. Therefore, we translated the estimated mean pre-control nodule prevalence to mf prevalence (standardized to 5+ population of the OCP reference population), based on a simple association derived from previously published data (Figure B.2; Remme 2004). The association between nodule prevalence and mf prevalence was characterized for mesoendemic and hyperendemic areas as follows:

$$\text{for } p_{nod} \geq 20\,\% \text{ and } < 40\,\%\text{:} \qquad p_{mf} = p_{nod} + 20 \tag{B.1}$$

$$\text{for } p_{nod} \geq 40\,\%\text{:} \qquad p_{mf} = \frac{3}{4}(p_{nod} + 40) \tag{B.2}$$

where p_{mf} and p_{nod} represent standardized mf prevalence and nodule prevalence in adult males, respectively.

Based on an analysis of the REMO data, combined with the translation of nodule prevalence to mf prevalence described above, we assumed that the mean pre-control, standardized mf prevalences in mesoendemic and hyperendemic areas were 49 % and 76 % respectively (corresponding to nodule prevalences of 29 % and 61 %, respectively). These mf prevalences were simulated in ONCHOSIM, using parameter values in Table B.1. We assumed that the variability in exposure was higher when the average monthly biting rate was lower. This association was based on earlier unpublished work done by Anton Plaisier; when he compared data from Folonzo, Tiercoura and Asubende (Ghana); relatively low-endemic situations could only be simulated with a combination of low relative biting rates and high exposure heterogeneity. A description of the technical implementation of these parameters can be reviewed in an earlier publication (Plaisier et al. 1990).

Calibration of ONCHOSIM parameters for eye disease

Following the WHO criteria for blindness and visual impairment, we defined blindness as visual acuity of less than 3/60 or a restriction of visual field to less than 10° in the better eye. According to the same criteria, we defined visual impairment as visual acuity of less than 6/18 but better than 3/60 in the better eye. We assumed that blindness and visual impairment are irreversible conditions, which is supported by a Cochrane review of placebo-controlled trials that found no statistically significant effect of ivermectin on functional vision loss (Ejere, Schwartz, and Wormald 2001), even though some early eye lesions may respond to ivermectin treatment (Abiose 1998). We assumed that blindness reduces the remaining life expectancy by 50 %, based on trends in blindness in OCP in West Africa (S6) (Dadzie et al. 1986). For visual impairment we assumed no reduction in life expectancy.

ONCHOSIM predicts the development of eye disease as a function of cumulative exposure to infection, reflecting an accumulation of damage in the eye. If a simulated individual's cumulative mf-count passes a critical threshold level, he or she turns visually impaired

or blind. In ONCHOSIM, the actual threshold is assumed to vary randomly between individuals, reflecting variation in individual susceptibility. Further, ONCHOSIM models excess mortality due to blindness by reducing the remaining life expectancy of people who have turned blind by a mean factor, again allowing some individual variation.

In ONCHOSIM, visual impairment and blindness could not be modeled simultaneously (i.e. it was possible to define one threshold for cumulative exposure to infection at a time). Therefore, we first modeled blindness; next, we modeled all visual impairment (including blindness) by lowering the value of the threshold. The excess mortality (specified as reduction in remaining life-expectancy) was adjusted accordingly. The prevalence of visual impairment, excluding blindness, was estimated by subtracting the predicted prevalence of blindness from the predicted prevalence of all visual impairment (including blindness). Because visual impairment and blindness were modeled in separate simulations, the simulated populations with blindness and visual impairment were not exactly comparable. However, differences were not large, and were deemed acceptable.

It is commonly accepted that the severity of eye disease is different for the forest and savanna types of onchocerciasis. Therefore, the thresholds for blindness and visual impairment were determined separately for savanna and forest areas. Excess mortality among blind people was assumed to be equal in forest and savanna areas.

Disease threshold and excess mortality for savanna type of onchocerciasis

For onchocercal blindness in savanna areas, we calibrated ONCHOSIM using published data from OCP (Remme et al. 1989). To fit a threshold value for blindness to these data, we varied the threshold and model parameters for transmission (relative biting rate and the associated exposure heterogeneity) over a wide range of values and compared the observed (OCP data) and model-predicted association between prevalence of mf and blindness (or visual impairment) in a standardized population of five years and older. A good fit for savanna blindness was obtained with a disease threshold for the cumulative mf count of 4,000 (Figure B.3).

Because in contrast to blindness, there was little literature data available about the association between visual impairment and mf prevalence in savanna areas, we based the threshold for visual impairment on a documented ratio of visual impairment and blindness in savanna areas. In pre-control, hyperendemic savanna areas of OCP, the pre-control prevalence of visual impairment has been reported to be 1.8 times the prevalence of blindness (Remme 2004). This pattern was reproduced in ONCHOSIM with a threshold value of 2800. With this value, the predicted prevalence of eye disease (i.e. visual impairment) was 1.8 times the predicted prevalence of blindness, at mf prevalence of 73 % (which was the mean prevalence of infection in hyperendemic OCP areas).

The parameter value for excess mortality (reduction in remaining life expectancy) was based on OCP data on trends in blindness during vector control. Part of these data (first 7–8 years) have been previously published (Dadzie et al. 1986); additional follow-up data were kindly provided by Dr Y. Dadzie. The data pertain to ten villages in Burkina Faso, Côte d'Ivoire and Ghana for which longitudinal data was available and history of vector control was known. In these villages, the pre-control mf prevalence was between 70 % and 90 %. Assuming that vector control reduced the biting rate to zero (an assumption previously used to successfully predict the impact of the OCP (Plaisier et al. 1997)), we used ONCHOSIM to predict the trend in prevalence of blindness (Figure B.4). This was done for several values of the relative biting rate and exposure heterogeneity that predict mf prevalences between 70 % and 90 % (top and bottom dashed lines in Figure B.4). The mean trend of blindness in these simulations was compared to the data for a range of parameter values for excess mortality due to blindness. A mean 50 % reduction in remaining life expectancy in blind people could adequately predict the observed trend in the OCP data. This value was allowed to vary between individuals (uniform distribution, range 0–100 %).

In simulations for visual impairment including blindness, the parameter for excess mortality was set to 20 % (uniform distribution, range 0–40 %). Assuming that there is no excess mortality in people with low vision, and taking account of the fact that the number of

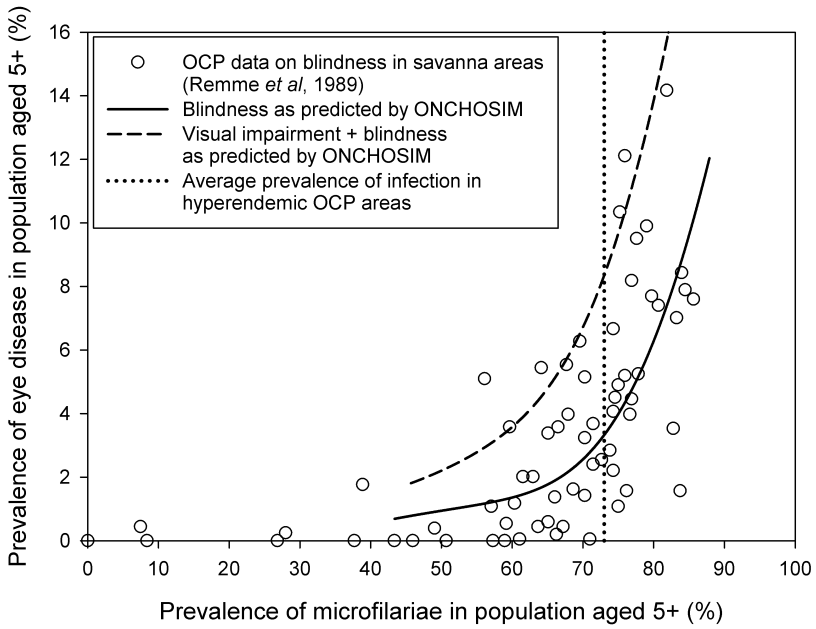

Figure B.3: Goodness-of-fit of ONCHOSIM to OCP data on the association between infection and blindness and visual impairment in savanna areas. Blindness data were obtained from Remme et al (1989). For visual impairment, ONCHOSIM was calibrated so that the prevalence of visual impairment was 1.8 times the prevalence of blindness in hyperendemic areas, represented by mf prevalence 73 % (Remme 2004).

people with low vision is 1.8 times the number of blind people, 20 % is roughly equal to 50 % times $1.0/(1.0 + 1.8)$.

Disease threshold for forest/mixed type of onchocerciasis

There is less information about the association between infection and blindness for the forest type of onchocerciasis than for the savannah type. Considering that the prevalence of blindness and visual impairment is much lower in forest/mixed areas than in savannah areas, for the entire range of mf prevalences, we need higher disease thresholds. We took the following approach in calibrating the

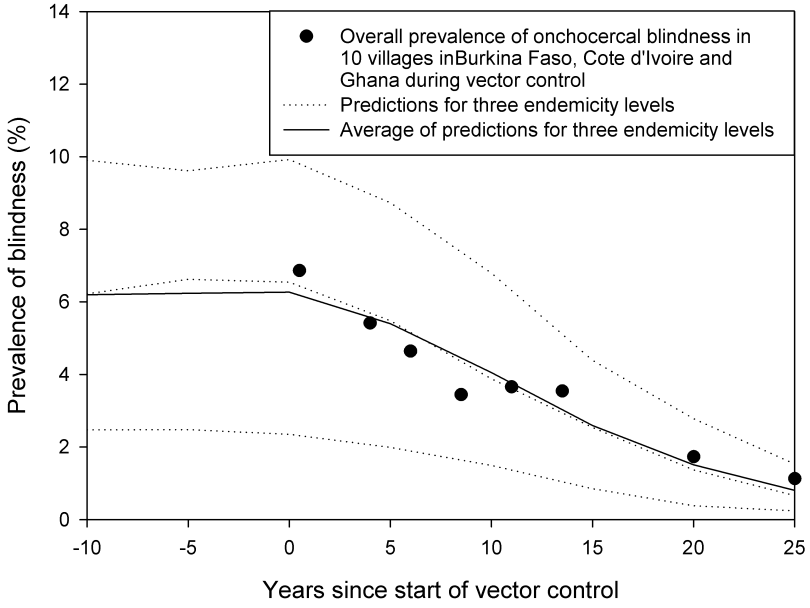

Figure B.4: Trend in prevalence of blindness in the original OCP area and the trend as predicted by ONCHOSIM, assuming that the remaining life expectancy is halved at onset of blindness. See text for further explanation. Data for the first 7–8 years have been previously published (Dadzie et al. 1986); additional follow-up data were kindly provided by Dr K.Y. Dadzie.

disease threshold for the forest/mixed type of onchocerciasis.

We collated available literature data on onchocercal blindness and infection in non-savanna areas (forest and mixed forest-savanna areas; Brown and Shannon 1989; Henry and Maertens 1990; Whitworth et al. 1991a, 1993; Kayembe et al. 2003; Remme 2004; Resnikoff et al. 2004). Because the literature data varied with respect to the methods to measure blindness, the age groups in which blindness prevalence was measured and the indicator of infection (microfilariae in the skin or palpable nodules), we standardized the data before calibrating ONCHOSIM. In many studies only the central vision was tested whereas onchocerciasis also affects the peripheral vision. According to the WHO criteria, persons can also be functionally blind if the peripheral vision is affected. When this was not taken into account, we multiplied the reported prevalence of blind-

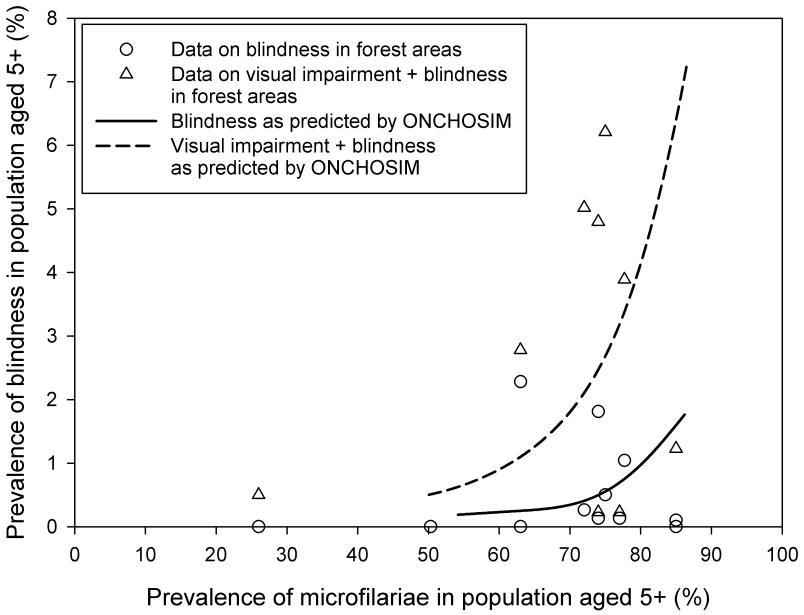

Figure B.5: Goodness-of-fit of ONCHOSIM to data on the association between infection and blindness and visual impairment in forest and mixed forest / savanna areas.

ness by 4/3, assuming that 25 % of functional blindness had been missed, as previously estimated (Remme 2004). If reported blindness was due to any cause, a background prevalence of non-onchocercal blindness of 0.96 % was assumed, as previously estimated (Resnikoff et al. 2004). If nodule prevalence in adult males was reported, we translated it to mf prevalence in the general population, using the association described in section S5. Next, we fitted the threshold levels for blindness and low vision in ONCHOSIM to the standardized data. The parameters for excess mortality among the blind and the association between biting rate and exposure heterogeneity were assumed equal to the model calibration for the savanna areas. A good fit was obtained with a threshold value of 10,000 for blindness and of 5,500 for visual impairment. The goodness-of-fit is shown in Figure B.5.

Calibration of model parameters for troublesome itch

We estimated the prevalence of itch from the prevalence of infection, as predicted by ONCHOSIM. For the pre-control situation, we could have simply related the prevalence of itch to the prevalence of microfilariae, assuming that itch is a direct effect of the presence of microfilariae in the skin; empirical data are available about this relationship. However, from ivermectin trials we learn that this direct link between presence of mf and itch does not hold during ivermectin treatment; prevalence and skin load of microfilariae in the population drop sharply almost instantly after treatment, whereas the reduction in prevalence of itch is smaller and moreover, delayed compared to the drop in mf load and prevalence (Brieger et al. 1998). This means that after ivermectin treatment, some people can still experience itch, even though there microfilarial loads have dropped drastically. Furthermore, this means that linking itch to microfilaria as predicted by ONCHOSIM is probably not the best way to predict trends in itch. Because adult worms have a longer life span than microfilariae and because ivermectin treatment does not (or only marginally) affect adult worm viability, we linked itch to the presence of adult worms in the body. Because at this point we have not yet accounted for the effect of ivermectin on itch, we refer to this predicted prevalence of itch as 'potential' prevalence of itch, referring to the prevalence of itch in the fraction of the population which has not participated in mass treatment in a given year. For the fraction of the population that was actually treated with ivermectin, we corrected the potential prevalence of itch for the effect of ivermectin, based on literature data.

The association between prevalence of adult female worms and itch was analyzed in the following steps. First, we determined the statistical association between nodule prevalence in adult males and potential prevalence of itch in the general population, based on data from a multi-country study (Murdoch et al. 2002). Second, we determined the statistical association between prevalence of adult female worms and potential prevalence of itch in the general population by substituting nodule prevalence for standardized mf prevalence

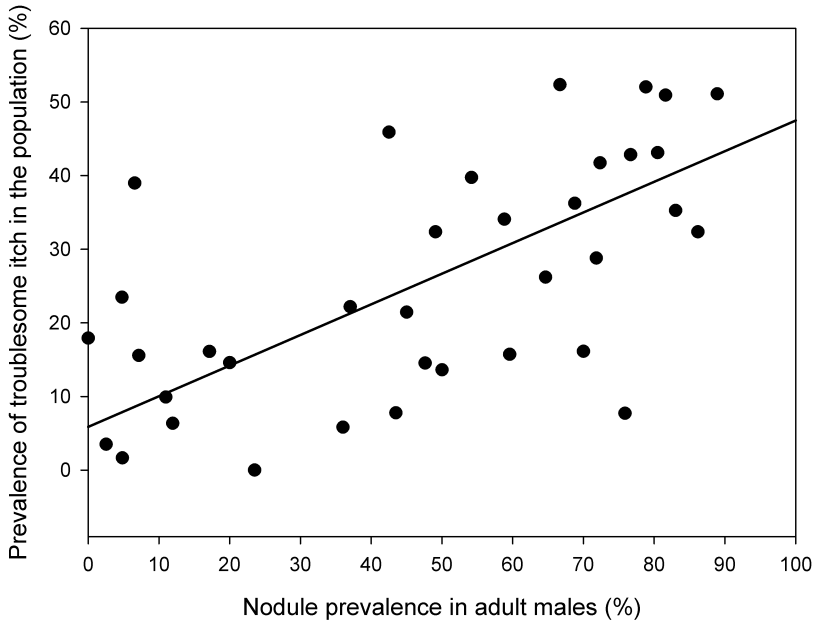

Figure B.6: The association between nodule prevalence in adult males (x-axis) and the prevalence of troublesome itch (y-axis), based on standardized data (bullets) from previously published work by Murdoch et al. (2002). The regression line representing the association was estimated by means of orthogonal regression, assuming that the variance of the measurement errors in nodule prevalence and prevalence of troublesome itch were equal ($\lambda = 1$).

(based on the association between the two as described in S5), and next substituting standardized mf prevalence for prevalence of adult female worms (based on the association between the two as predicted by ONCHOSIM). Last, we determined the average year-round reduction in prevalence of itch in treated individuals, based on literature (Brieger et al. 1998).

Statistical association between nodule prevalence and itch

Using data from a multi-country study on prevalence of infection and skin-disease, we estimated the association between nodule preva-

lence and the prevalence of troublesome itch for the forest-type of onchocerciasis (Murdoch et al. 2002). As there is no evidence for a difference in patterns of itch between savanna and forest areas, and for lack of data, we assumed that this association also holds in savanna areas. We re-analyzed the original raw data to obtain village-specific estimates for the nodule prevalence in adult males and the prevalence of itch in the whole population. Estimates of the nodule prevalence in adult males could be readily obtained from the data. However, the crude estimates of troublesome itch in the whole population were biased because younger age groups were underrepresented and elderly were overrepresented in the data. Therefore, we standardized the data to the United Nations World Population Prospects standard population for Sub Sahara Africa (2003 Revision). The standardized prevalence levels were always lower than the crude ones.

Next, the age-standardized data were further analyzed to estimate the background prevalence of itch at zero prevalence of infection (i.e. prevalence of itch that is not caused by onchocerciasis). A regression line was fitted to the data by means of orthogonal linear regression (Figure B.6). This regression method corrects (to some extent) for non-systematic misclassification of exposure (nodule prevalence), which leads to dilution-bias in case of ordinary linear regression. Ignoring this non-systematic misclassification would lead to an underestimation of the strength of the relationship between onchocerciasis infection and itch and an inflated estimate of the background non-onchocercal itch. In orthogonal regression, the correction for dilution-bias is based on a (assumed) ratio (λ) of the measurement error (variance) in the exposure and outcome variables. We assumed that the variance of the measurement errors in nodule prevalence and prevalence of troublesome itch were equal ($\lambda = 1$). The slope of the regression line was estimated at 0.416 (increase in potential prevalence of itch for every 1 % increase in nodule prevalence); the intercept was estimated at 5.888 (background prevalence of itch).

The background prevalence of itch was therefore estimated at 5.9 %. However, we also wanted to take into account that some of the people with itch from other causes may in addition suffer

from onchocercal itch. Therefore, we did not simply subtract the 5.9 % background prevalence from the estimated prevalence of all-cause itch. Instead, we assumed that in addition to the predicted prevalence of potential onchocercal itch, a certain proportion of people suffering from itch due to other causes suffered (partly) from onchocercal itch. This proportion was assumed to be equal to the prevalence of onchocercal itch in the population without itch from other causes, leading to the following equation for total predicted prevalence of potential itch: slope × nodule prevalence × 100/(100 − intercept).

The association between prevalence of itch and adult female worms

As mentioned earlier, we linked the association between nodule prevalence in adult males and itch in the general population to ONCHOSIM predictions for standardized mf prevalence in the population aged five and above, using the known association between nodule prevalence and mf prevalence (S5). By calculating the prevalence of itch for a range of simulated mf prevalences, and plotting these prevalences of itch against the concomitantly simulated prevalences of adult female worms, we could determine a statistical association between prevalence of itch and adult female worms in the general population (Figure B.7).

Note that the simulated itch prevalence was almost linearly related to the prevalence of adult worms. However, as ONCHOSIM predicts that independently sustained transmission of infection in hypoendemic areas is impossible, we could not calculate prevalences of itch for situations that corresponded with low prevalence of adult female worms. Instead, we assumed that the regression line for this association passes through the origin, using the following equation:

$$p_{itch} = a \times p_{worms} + b \times \left(1 - \exp\left((p_{worms}/100)^2\right)\right) \qquad \text{(B.3)}$$

where pitch and pworms are prevalence of itch and adult female worms (0–100 % scale), respectively. The values of parameters a and b were estimated at -0.043 and -45.532, respectively. For prevalence of adult female worms close to zero, this equation can

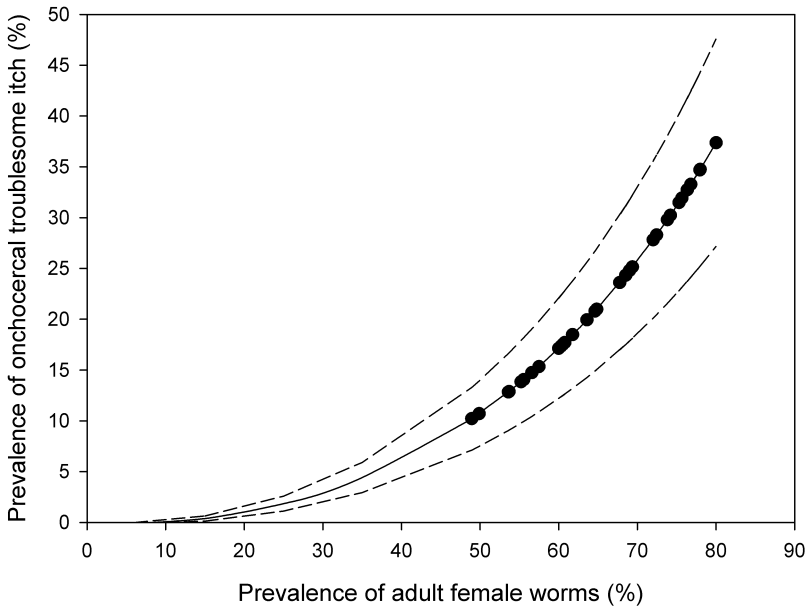

Figure B.7: The modeled relationship between prevalence of adult female worms and onchocerciasis-related troublesome itch in the population. Bullets represent ONCHOSIM predictions for prevalence of adult female worms and the associated itch, calculated from the concomitantly predicted standardized prevalence of microfilariae in the skin. The association between prevalence of adult female worms and itch (solid line) was determined by means of non-linear regression. In the sensitivity analysis, parameter b was allowed to vary by ±25 %, resulting in a stronger or weaker association between prevalence of adult worms and prevalence of onchocerciasis-related troublesome itch (dashed lines).

take on negative values; in that case, we assumed that the itch prevalence was zero.

Using this final equation, we predicted the 'potential' prevalence of itch in the general population, based on its current status of infection (prevalence of adult female worms) and as if it had not (yet) been treated with ivermectin during that year.

The effect of ivermectin on prevalence of itch

Based on literature (Brieger et al. 1998), we assumed that ivermectin reduces the average year-round prevalence of itch by 30 % in treated individuals. This figure is based on the observed pattern in the relative reduction of prevalence of itch at 3, 6, 9, and 12 months after a single treatment of ivermectin. When plotting the relative reduction of prevalence of itch over time (relative reduction of 5.6 %, 44.9 %, 46.3 %, and 31 %, respectively) and connecting these data points with straight lines, the area under the curve was approximately 30 %, representing the average year-round reduction in prevalence of itch due to ivermectin.

The estimated prevalence of itch among treated individuals was calculated by first calculating the 'potential' prevalence of itch, based on predicted prevalence of adult female worms just before mass treatment (which was assumed to take place at the start of the year), and multiplying it with 0.7 (30 % reduction). The average year-round prevalence of itch among non-treated individuals was estimated from the mid-year prevalence of adult female worms, without correction for an effect of ivermectin. Finally, the average year-round prevalences of itch in the treated and untreated fractions of the population were averaged, weighted for the size of each population fraction.

Calculation of the burden of disease

For each year, we calculated the number of disability adjusted life years (DALYs) lost due to onchocerciasis in the APOC area, as the sum of years of life lived in disability (YLD) and year of life lost (YLL) due to excess mortality from blindness. YLD were calculated by multiplying number of prevalent cases with previously published disability weights; i.e. 0.594 for blindness, 0.282 for visual impairment and 0.068 for troublesome itch (WHO 2004). YLL apply to blindness only and were calculated based on incident cases of blindness (i.e. lost future life years). The annual number of incident cases of blindness was calculated as the difference between the number of blind cases in year t and the number of blind cases in year $(t-1)$ that were expected to have survived up to year t, based on the average remaining life-expectancy at onset of blindness.

The latter was estimated by determining the average age of onset of blindness in ONCHOSIM (in a situation without mass treatment), and calculating the associated average remaining life-expectancy for a healthy person (which was 16 years), and combining this with the 50 % reduction in life-expectancy due to blindness. Consequently, every incident case of blindness was assumed to have an average remaining life expectancy of 8 years, meaning that 7 out of 8 prevalent cases of blindness were assumed to survive each year. Also following from this, every incident case of blindness was attributed 8 YLL in terms of burden of disease.

Sensitivity analysis

To investigate the impact of model assumptions on the estimated health impact, we performed univariate and multivariate sensitivity analyses. We included model assumptions that were expected to possibly have an important impact on the estimated health impact. In the univariate sensitivity analysis, we repeated the original analysis, but with (plausible) extreme values for each of the following model and data-derived parameters (extreme values between brackets): size of population at risk (±10%), pre-control levels of infection (±10%), therapeutic coverage (±10%), the association between exposure to infection and development of eye disease (±25% in the required cumulative exposure to infection for development of eye disease, Figure B.8), the association between prevalence of adult female worms and troublesome itch (parameter b ±25%, Figure B.8), effect of ivermectin on adult female worms (26 % or 40 % permanent reduction in fecundity, instead of 35 %, based on a previously published 95 %-confidence interval for this parameter value (Plaisier et al. 1995)), effect of ivermectin on itch (reduction in prevalence of 20 % or 40 %, instead of 30 %), the years of life lost per incident case of blindness (6 or 10 years, instead of 8), and levels of infection and morbidity in hypoendemic areas as fraction of mesoendemic areas (1/10 or 1/2, instead of 1/3).

In the multivariate sensitivity analysis, we repeated the original analysis 200 times, while letting all selected parameters vary in each analysis. This analysis allowed for possible interaction between pa-

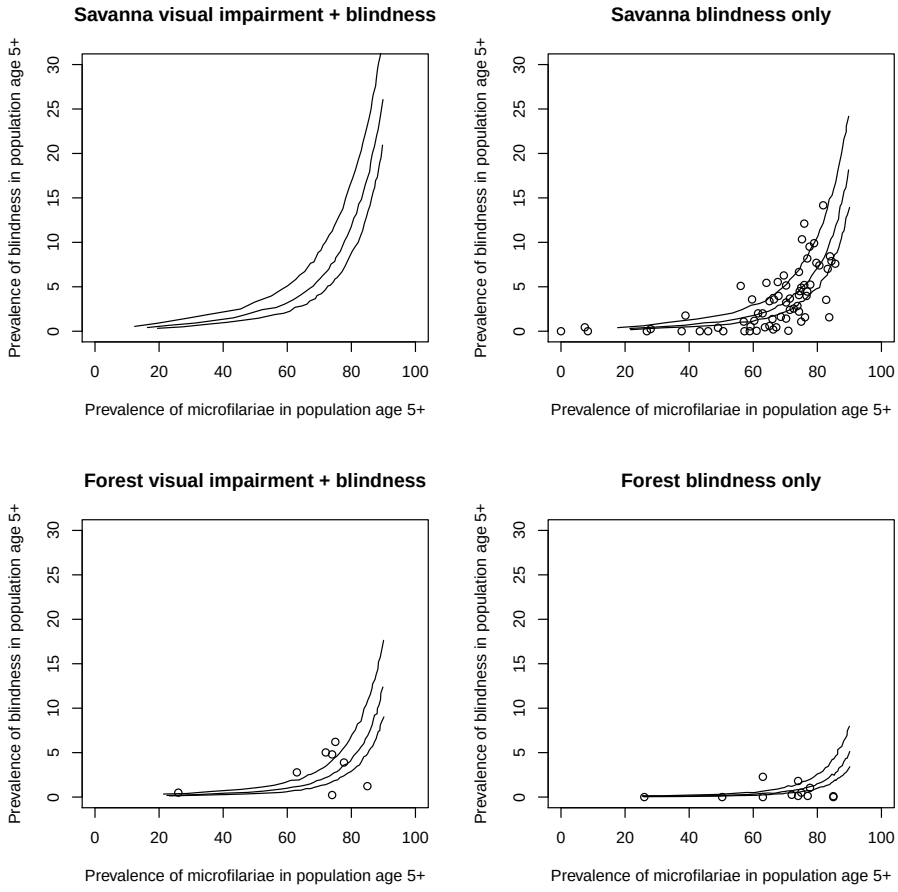

Figure B.8: Association between prevalence of infection and eye disease as predicted by ONCHOSIM in the main analysis (middle line in each panel) and the univariate sensitivity analysis (outer lines in each plot), compared to the data (open circles). For the univariate sensitivity analysis it was assumed that the required cumulative exposure to infection for the development of eye disease was 25 % lower or higher than assumed in the main analysis.

rameters; e.g. lower mass treatment coverage combined with higher pre-control infection levels might result in a drastically lower estimated health impact. Parameter values were varied by randomly drawing values from triangular distributions, which were defined by a mode equal to the parameter value used in the main analysis, and minimum and maximum values equal to the extreme values used in the univariate sensitivity analysis. Assuming that these triangular distributions are an adequate reflection of the uncertainty in the parameter values, we made a crude estimate of the uncertainty in the estimated health impact of APOC by taking the 2.5^{th} and 97.5^{th} percentiles of the results from the 200 repeated analyses.

Bibliography

Abedin S, Narang M, Gandhi V, and Narang S (2007). Efficacy of permethrin cream and oral ivermectin in treatment of scabies. *Indian J Pediatr* 74.10, 915–916 (cit. on p. 102).

Abiose A (1998). Onchocercal eye disease and the impact of Mectizan treatment. *Ann Trop Med Parasitol* 92 Suppl 1, S11–S22 (cit. on p. 172).

Addiss D and The Global Alliance to Eliminate Lymphatic Filariasis (2010). The 6th Meeting of the Global Alliance to Eliminate Lymphatic Filariasis: A half-time review of lymphatic filariasis elimination and its integration with the control of other neglected tropical diseases. *Parasit Vectors* 3 (100). DOI: 10.1186/1756-3305-3-100 (cit. on p. 150).

Adler PH, Cheke RA, and Post RJ (2010). Evolution, epidemiology, and population genetics of black flies (Diptera: Simuliidae). *Infect Genet Evol* 10.7, 846–865. DOI: 10.1016/j.meegid.2010.07.003 (cit. on p. 2).

Albers A, Esum ME, Tendongfor N, Enyong P, Klarmann U, Wanji S, Hoerauf A, and Pfarr K (2012). Retarded *Onchocerca volvulus* L1 to L3 larval development in the *Simulium damnosum* vector after anti-wolbachial treatment of the human host. *Parasit Vectors* 5, 12. DOI: 10.1186/1756-3305-5-12 (cit. on pp. 10, 148).

Albiez EJ (1983). Studies on nodules and adult *Onchocerca volvulus* during a nodulectomy trial in hyperendemic villages in Liberia and Upper Volta. I. Palpable and impalpable onchocercomata. *Tropenmed Parasitol* 34.1, 54–60 (cit. on p. 8).

Albiez EJ (1985). Effects of a single complete nodulectomy on nodule burden and microfilarial density two years later. *Trop Med Parasitol* 36.1, 17–20 (cit. on p. 9).

Albiez EJ, Büttner DW, and Duke BO (1988). Diagnosis and extirpation of nodules in human onchocerciasis. *Trop Med Parasitol* 39 Suppl 4, 331–346 (cit. on pp. 8, 30).

Albiez EJ, Walter G, Kaiser A, Ranque P, Newland HS, White AT, Greene BM, Taylor HR, and Büttner DW (1988). Histological examination of onchocercomata after therapy with ivermectin. *Trop Med Parasitol* 39.2, 93–99 (cit. on p. 8).

Albonico M, Allen H, Chitsulo L, Engels D, Gabrielli A.-F, and Savioli L (2008). Controlling soil-transmitted helminthiasis in pre-school-age children through preventive chemotherapy. *PLoS Negl Trop Dis* 2.3, e126. DOI: 10.1371/journal.pntd.0000126 (cit. on pp. 100, 101).

Ali MMM, Elghazali G, Montgomery SM, Farouk SE, Nasr A, Noori SIA, Shamad MM, Fadlelseed OE, and Berzins K (2007). Fc gamma RIIa (CD32) polymorphism and onchocercal skin disease: implications for the development of severe reactive onchodermatitis (ROD). *Am J Trop Med Hyg* 77.6, 1074–1078 (cit. on p. 43).

Alley ES, Plaisier AP, Boatin BA, Dadzie KY, Remme J, Zerbo G, and Samba EM (1994). The impact of five years of annual ivermectin treatment on skin microfilarial loads in the onchocerciasis focus of Asubende, Ghana. *Trans R Soc Trop Med Hyg* 88.5, 581–584 (cit. on pp. 18, 79, 80, 115–117).

Alonso L, Murdoch M, and Jofre-Bonet M (2009). Psycho-social and economical evaluation of onchocerciasis: a literature review. *Soc Med* 4.1, 8–31 (cit. on pp. 10, 59, 76).

Amazigo U (2008). The African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol* 102 Suppl 1, 19–22. DOI: 10.1179/136485908X337436 (cit. on pp. 13, 95, 113, 132).

Amazigo UO (1994). Detrimental effects of onchocerciasis on marriage age and breast-feeding. *Trop Geogr Med* 46.5, 322–325 (cit. on p. 11).

Anderson J and Fuglsang H (1977). Ocular onchocerciasis. *Trop Dis Bull* 74.4, 257–272 (cit. on p. 3).

Anderson J, Fuglsang H, Hamilton PJ, and de Marshall TF (1974a). Studies on onchocerciasis in the United Cameroon Republic. I. Comparison of populations with and without *Onchocerca volvulus*. *Trans R Soc Trop Med Hyg* 68.3, 190–208 (cit. on p. 43).

Anderson J, Fuglsang H, Hamilton PJ, and de Marshall TF (1974b). Studies on onchocerciasis in the United Cameroon Republic. II. Comparison of onchocerciasis in rain-forest and Sudan-savanna. *Trans R Soc Trop Med Hyg* 68.3, 209–222 (cit. on pp. 4, 43).

Anderson J, Fuglsang H, and al-Zubaidy A (1973). Onchocerciasis in Yemen with special reference to sowda. *Trans R Soc Trop Med Hyg* 67.1, 30–31 (cit. on p. 4).

Andrews G, Sanderson K, and Beard J (1998). Burden of disease. Methods of calculating disability from mental disorder. *Br J Psychiatry* 173, 123–131 (cit. on pp. 50, 59).

Anosike JC, Dozie INS, Ameh GI, Ukaga CN, Nwoke BEB, Nzechukwu CT, Udujih OS, and Nwosu DC (2007). The varied beneficial effects of ivermectin (Mectizan) treatment, as observed within onchocerciasis foci in south-eastern Nigeria. *Ann Trop Med Parasitol* 101.7, 593–600. DOI: 10.1179/136485907X229022 (cit. on pp. 95, 100, 102).

APOC (2009). *Year 2009 progress report*. World Health Organization (cit. on p. 43).

APOC (2010). *Conceptual and operational framework of onchocerciasis elimination with ivermectin treatment*. Tech. rep. World Health Organization (cit. on pp. 16, 113, 140, 148).

Awadzi K, Attah SK, Addy ET, Opoku NO, and Quartey BT (1999). The effects of high-dose ivermectin regimens on *Onchocerca volvulus* in onchocerciasis patients. *Trans R Soc Trop Med Hyg* 93.2, 189–194 (cit. on p. 76).

Awadzi K, Attah SK, Addy ET, Opoku NO, Quartey BT, Lazdins-Helds JK, Ahmed K, Boatin BA, Boakye DA, and Edwards G (2004a). Thirty-month follow-up of sub-optimal responders to multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. *Ann Trop Med Parasitol* 98.4, 359–370. DOI: 10.1179/000349804225003442 (cit. on p. 149).

Awadzi K, Boakye DA, Edwards G, Opoku NO, Attah SK, Osei-Atweneboana MY, Lazdins-Helds JK, Ardrey AE, Addy ET, Quartey BT, Ahmed K, Boatin BA, and Soumbey-Alley EW (2004b). An investigation of persistent microfilaridermias despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. *Ann Trop Med Parasitol* 98.3, 231–249. DOI: 10.1179/000349804225003253 (cit. on p. 149).

Awadzi K, Hero M, Opoku NO, Addy ET, Büttner DW, and Ginger CD (1995). The chemotherapy of onchocerciasis XVIII. Aspects of treatment with suramin. *Trop Med Parasitol* 46.1, 19–26 (cit. on p. 9).

Awadzi K (2003). Clinical picture and outcome of Serious Adverse Events in the treatment of Onchocerciasis. *Filaria J* 2 Suppl 1, S6. DOI: 10.1186/1475-2883-2-S1-S6 (cit. on pp. 9, 148).

Babalola OE, Maegga B, Katenga S, Ogbuagu FK, Umeh RE, Seketeli E, and Braide E (2008). APOC impact assessment studies: baseline ophthalmological findings in Morogoro, Tanzania. *Afr J Med Med Sci* 37.4, 327–332 (cit. on p. 47).

Babalola OE, Ogbuagu FK, Maegga BT, Braide EI, Magimbi C, Zoure H, Yameogo L, and Seketeh A (2011). African programme for Onchoceriasis control: ophthalmological findings in Bushenyi, Uganda. *West Afr J Med* 30.2, 104–109 (cit. on p. 36).

Badiaga S, Foucault C, Rogier C, Doudier B, Rovery C, Dupont HT, Castro P, Raoult D, and Brouqui P (2008). The effect of a single dose of oral ivermectin on pruritus in the homeless. *J Antimicrob Chemother* 62.2, 404–409. DOI: 10.1093/jac/dkn161 (cit. on p. 102).

Basáñez MG and Ricárdez-Esquinca J (2001). Models for the population biology and control of human onchocerciasis. *Trends Parasitol* 17.9, 430–438 (cit. on p. 17).

Basáñez M.-G, Churcher TS, and Grillet M.-E (2009). Onchocerca-Simulium interactions and the population and evolutionary biology of *Onchocerca volvulus*. *Adv Parasitol* 68, 263–313. DOI: 10.1016/S0065-308X(08)00611-8 (cit. on pp. 2, 145).

Basáñez M.-G, Collins RC, Porter CH, Little MP, and Brandling-Bennett D (2002). Transmission intensity and the patterns of *Onchocerca volvulus* infection in human communities. *Am J Trop Med Hyg* 67.6, 669–679 (cit. on p. 146).

Basáñez M.-G, Pion SDS, Boakes E, Filipe JAN, Churcher TS, and Boussinesq M (2008). Effect of single-dose ivermectin on *Onchocerca volvulus*: a systematic review and meta-analysis. *Lancet Infect Dis* 8.5, 310–322. DOI: 10.1016/S1473-3099(08)70099-9 (cit. on pp. 9, 65, 116, 119).

Basáñez M.-G, Pion SDS, Churcher TS, Breitling LP, Little MP, and Boussinesq M (2006). River blindness: a success story under threat? *PLoS Med* 3.9, e371. DOI: 10.1371/journal.pmed.0030371 (cit. on p. 3).

Belizario VY, Amarillo ME, de Leon WU, de los Reyes AE, Bugayong MG, and Macatangay BJC (2003). A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against Ascaris and Trichuris spp. *Bull World Health Organ* 81.1, 35–42 (cit. on p. 100).

Benton B (1998). Economic impact of onchocerciasis control through the African Programme for Onchocerciasis Control: an overview. *Ann Trop Med Parasitol* 92 Suppl 1, S33–S39 (cit. on pp. 11, 81).

Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, and Hotez PJ (2006). Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 367.9521, 1521–1532. DOI: 10.1016/S0140-6736(06)68653-4 (cit. on pp. 95, 100, 101).

Bird AC, Anderson J, and Fuglsang H (1976). Morphology of posterior segment lesions of the eye in patients with onchocerciasis. *Br J Ophthalmol* 60.1, 2–20 (cit. on p. 3).

Boatin B (2008). The Onchocerciasis Control Programme in West Africa (OCP). *Ann Trop Med Parasitol* 102 Suppl 1, 13–17. DOI: 10.1179/136485908X337427 (cit. on pp. 12, 65).

Boatin BA, Toé L, Alley ES, Nagelkerke NJD, Borsboom G, and Habbema JDF (2002). Detection of *Onchocerca volvulus* infection in low prevalence areas: a comparison of three diagnostic methods. *Parasitology* 125.Pt 6, 545–552 (cit. on p. 8).

Bottomley C, Isham V, Collins RC, and Basáñez M.-G (2008). Rates of microfilarial production by *Onchocerca volvulus* are not cumulatively reduced by multiple ivermectin treatments. *Parasitology* 135.13, 1571–1581. DOI: 10.1017/S0031182008000425 (cit. on pp. 9, 80).

Bourguinat C, Pion SDS, Kamgno J, Gardon J, Gardon-Wendel N, Duke BOL, Prichard RK, and Boussinesq M (2006). Genetic polymorphism of the beta-tubulin gene of *Onchocerca volvulus* in ivermectin naïve patients from Cameroon, and its relationship with fertility of the worms. *Parasitology* 132.Pt 2, 255–262. DOI: 10.1017/S0031182005008899 (cit. on p. 149).

Bourguinat C, Pion SDS, Kamgno J, Gardon J, Duke BOL, Boussinesq M, and Prichard RK (2007). Genetic selection of low fertile

Onchocerca volvulus by ivermectin treatment. *PLoS Negl Trop Dis* 1.1, e72. DOI: 10.1371/journal.pntd.0000072 (cit. on p. 149).

Boussinesq M (2006). Loiasis. *Ann Trop Med Parasitol* 100.8, 715–731. DOI: 10.1179/136485906X112194 (cit. on pp. 9, 148).

Boussinesq M, Gardon J, Gardon-Wendel N, and Chippaux J.-P (2003). Clinical picture, epidemiology and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. *Filaria J* 2 Suppl 1, S4. DOI: 10.1186/1475-2883-2-S1-S4 (cit. on p. 107).

Boussinesq M, Kamgno J, Pion SD, and Gardon J (2006). What are the mechanisms associated with post-ivermectin serious adverse events? *Trends Parasitol* 22.6, 244–246. DOI: 10.1016/j.pt.2006.04.006 (cit. on p. 108).

Brattig NW (2004). Pathogenesis and host responses in human onchocerciasis: impact of Onchocerca filariae and Wolbachia endobacteria. *Microbes Infect* 6.1, 113–128 (cit. on pp. 4, 43).

Brattig NW, Tischendorf FW, Reifegerste S, Albiez EJ, and Berger J (1986). Differences in the distribution of HLA antigens in localized and generalized form of onchocerciasis. *Trop Med Parasitol* 37.3, 271–275 (cit. on p. 43).

Brieger WR, Awedoba AK, Eneanya CI, Hagan M, Ogbuagu KF, Okello DO, Ososanya OO, Ovuga EB, Noma M, Kale OO, Burnham GM, and Remme JH (1998). The effects of ivermectin on onchocercal skin disease and severe itching: results of a multicentre trial. *Trop Med Int Health* 3.12, 951–961 (cit. on pp. 178, 179, 183).

Brooker S, Hotez PJ, and Bundy DAP (2010). The global atlas of helminth infection: mapping the way forward in neglected tropical disease control. *PLoS Negl Trop Dis* 4.7, e779. DOI: 10.1371/journal.pntd.0000779 (cit. on p. 95).

Brown R and Shannon R (1989). Prevalence, intensity and ocular manifestations of *Onchocerca volvulus* infection in Dimbelenge, Zaire. *Ann Soc Belg Med Trop* 69.2, 137–142 (cit. on p. 176).

Browne SG (1960). Onchocercal depigmentation. *Trans R Soc Trop Med Hyg* 54, 325–334 (cit. on p. 43).

Budden FH (1976). The natural history of ocular onchocerciasis over a period of 14–15 years and the effect on this of a single course of suramin therapy. *Trans R Soc Trop Med Hyg* 70.5-6, 484–491 (cit. on p. 3).

Burnham GM (1991). Onchocerciasis in Malawi. 1. Prevalence, intensity and geographical distribution of *Onchocerca volvulus* infection in the Thyolo highlands. *Trans R Soc Trop Med Hyg* 85.4, 493–496 (cit. on p. 43).

Burnham G (2007). Efficacy of ivermectin against *Onchocerca volvulus* in Ghana. *Lancet* 370.9593, 1125. DOI: 10.1016/S0140-6736(07)61505-0 (cit. on pp. 16, 149).

Büttner DW, Albiez EJ, von Essen J, and Erichsen J (1988). Histological examination of adult *Onchocerca volvulus* and comparison with the collagenase technique. *Trop Med Parasitol* 39 Suppl 4, 390–417 (cit. on p. 8).

Campbell WC (1991). Ivermectin as an antiparasitic agent for use in humans. *Annu Rev Microbiol* 45, 445–474. DOI: 10.1146/annurev.mi.45.100191.002305 (cit. on p. 95).

Carroll R, Ruppert D, Stefanski L, and Crainiceanu C (2006). Measurement error in nonlinear models: a modern perspective. Chapman and Hall. ISBN: 1584886331 (cit. on p. 28).

Centers for Disease Control and Prevention (CDC) (1995). Implementation of health initiatives during a cease-fire–Sudan, 1995. *MMWR Morb Mortal Wkly Rep* 44.23, 433–436 (cit. on p. 147).

Centers for Disease Control and Prevention (CDC) (2012). Nodding syndrome - South Sudan, 2011. *MMWR Morb Mortal Wkly Rep* 61.3, 52–54 (cit. on p. 6).

Cestari TF, Pessato S, and Ramos-e-Silva M (2007). Tungiasis and myiasis. *Clin Dermatol* 25.2, 158–164. DOI: 10.1016/j.clindermatol.2006.05.004 (cit. on p. 102).

Chaccour CJ, Kobylinski KC, Bassat Q, Bousema T, Drakeley C, Alonso P, and Foy BD (2013). Ivermectin to reduce malaria transmission: a research agenda for a promising new tool for elimination. *Malar J* 12, 153. DOI: 10.1186/1475-2875-12-153 (cit. on p. 107).

Chavasse DC, Post RJ, Davies JB, and Whitworth JA (1993). Absence of sperm from the seminal receptacle of female *Onchocerca*

volvulus following multiple doses of ivermectin. *Trop Med Parasitol* 44.3, 155–158 (cit. on pp. 116, 119).

Churcher TS and Basáñez M.-G (2009). Sampling strategies to detect anthelmintic resistance: the perspective of human onchocerciasis. *Trends Parasitol* 25.1, 11–17. DOI: 10.1016/j.pt.2008.09.011 (cit. on p. 149).

Churcher TS, Pion SDS, Osei-Atweneboana MY, Prichard RK, Awadzi K, Boussinesq M, Collins RC, Whitworth JA, and Basáñez M.-G (2009). Identifying sub-optimal responses to ivermectin in the treatment of River Blindness. *Proc Natl Acad Sci U S A* 106.39, 16716–16721. DOI: 10.1073/pnas.0906176106 (cit. on p. 149).

Coffeng LE, Fobi G, Ozoh G, Bissek AC, Nlatté BO, Enyong P, Olinga JMO, Zouré HGM, Habbema JDF, Stolk WA, de Vlas SJ, Boussinesq M, and Noma M (2012). Concurrence of dermatological and ophthalmological morbidity in onchocerciasis. *Trans R Soc Trop Med Hyg* 106.4, 243–251. DOI: 10.1016/j.trstmh.2011.12.006 (cit. on p. 137).

Coffeng LE, Pion SDS, O'Hanlon S, Cousens S, Abiose AO, Fischer PU, Remme JHF, Dadzie KY, Murdoch ME, de Vlas SJ, Basáñez M.-G, Stolk WA, and Boussinesq M (2013a). Onchocerciasis: the pre-control association between prevalence of palpable nodules and skin microfilariae. *PLoS Negl Trop Dis* 7.4, e2168. DOI: 10.1371/journal.pntd.0002168 (cit. on p. 137).

Coffeng LE, Stolk WA, Zouré HGM, Veerman JL, Agblewonu KB, Murdoch ME, Noma M, Fobi G, Richardus JH, Bundy DAP, Habbema D, de Vlas SJ, and Amazigo UV (2013b). African Programme for Onchocerciasis Control 1995-2015: model-estimated health impact and cost. *PLoS Negl Trop Dis* 7.1, e2032. DOI: 10.1371/journal.pntd.0002032 (cit. on pp. 23, 87, 88, 95, 97, 103, 113, 114, 116, 131, 136, 138–141).

Colatrella B (2008). The Mectizan Donation Program: 20 years of successful collaboration - a retrospective. *Ann Trop Med Parasitol* 102 Suppl 1, 7–11. DOI: 10.1179/136485908X337418 (cit. on p. 10).

Collins RC, Brandling-Bennett AD, Holliman RB, Campbell CC, and Darsie RF (1980). Parasitological diagnosis of onchocerciasis:

comparisons of incubation media and incubation times for skin snips. *Am J Trop Med Hyg* 29.1, 35–41 (cit. on p. 7).

Coulibaly Y, Cavalli A, van Dormael M, Polman K, and Kegels G (2008). Programme activities: a major burden for district health systems? *Trop Med Int Health* 13.12, 1430–1432. DOI: 10.1111/j.1365-3156.2008.02174.x (cit. on p. 132).

Cupp EW, Sauerbrey M, and Richards F (2011). Elimination of human onchocerciasis: history of progress and current feasibility using ivermectin (Mectizan(®)) monotherapy. *Acta Trop* 120 Suppl 1, S100–S108. DOI: 10.1016/j.actatropica.2010.08.009 (cit. on pp. 16, 113).

Cupp E, Richards F, Lammie P, and Eberhard M (2007). Efficacy of ivermectin against *Onchocerca volvulus* in Ghana. *Lancet* 370.9593, 1123, 1123, author reply 1125. DOI: 10.1016/S0140-6736(07)61501-3 (cit. on p. 149).

Cupp EW and Cupp MS (2005). Short report: impact of ivermectin community-level treatments on elimination of adult *Onchocerca volvulus* when individuals receive multiple treatments per year. *Am J Trop Med Hyg* 73.6, 1159–1161 (cit. on pp. 9, 116, 119).

Cupp EW, Duke BO, Mackenzie CD, Guzmán JR, Vieira JC, Mendez-Galvan J, Castro J, Richards F, Sauerbrey M, Dominguez A, Eversole RR, and Cupp MS (2004). The effects of long-term community level treatment with ivermectin (Mectizan) on adult *Onchocerca volvulus* in Latin America. *Am J Trop Med Hyg* 71.5, 602–607 (cit. on pp. 116, 119, 130).

Dadzie KY, De Sole G, and Remme J (1992). Ocular onchocerciasis and the intensity of infection in the community. IV. The degraded forest of Sierra Leone. *Trop Med Parasitol* 43.2, 75–79 (cit. on p. 3).

Dadzie KY, Remme J, Baker RH, Rolland A, and Thylefors B (1990). Ocular onchocerciasis and intensity of infection in the community. III. West African rainforest foci of the vector *Simulium sanctipauli*. *Trop Med Parasitol* 41.4, 376–382 (cit. on pp. 3, 23, 37).

Dadzie KY, Remme J, Rolland A, and Thylefors B (1986). The effect of 7-8 years of vector control on the evolution of ocular

onchocerciasis in West African savanna. *Trop Med Parasitol* 37.3, 263–270 (cit. on pp. 172, 174, 176).

Dadzie KY, Remme J, Rolland A, and Thylefors B (1989). Ocular onchocerciasis and intensity of infection in the community. II. West African rainforest foci of the vector *Simulium yahense*. *Trop Med Parasitol* 40.3, 348–354 (cit. on pp. 4, 23, 37).

Dadzie Y, Neira M, and Hopkins D (2003). Final report of the Conference on the eradicability of Onchocerciasis. *Filaria J* 2.1, 2 (cit. on pp. 23, 82, 131, 147).

Datry A, Hilmarsdottir I, Mayorga-Sagastume R, Lyagoubi M, Gaxotte P, Biligui S, Chodakewitz J, Neu D, Danis M, and Gentilini M (1994). Treatment of Strongyloides stercoralis infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Trans R Soc Trop Med Hyg* 88.3, 344–345 (cit. on p. 101).

Davies JB (1993). Description of a computer model of forest onchocerciasis transmission and its application to field scenarios of vector control and chemotherapy. *Ann Trop Med Parasitol* 87.1, 41–63 (cit. on p. 17).

de Silva NR, Guyatt HL, and Bundy DA (1997). Morbidity and mortality due to Ascaris-induced intestinal obstruction. *Trans R Soc Trop Med Hyg* 91.1, 31–36 (cit. on p. 100).

Dembélé M, Bamani S, Dembélé R, Traoré MO, Goita S, Traoré MN, Sidibe AK, Sam L, Tuinsma M, Toubali E, Macarthur C, Baker SK, and Zhang Y (2012). Implementing preventive chemotherapy through an integrated National Neglected Tropical Disease Control Program in Mali. *PLoS Negl Trop Dis* 6.3, e1574. DOI: 10.1371/journal.pntd.0001574 (cit. on p. 132).

Diawara L, Traoré MO, Badji A, Bissan Y, Doumbia K, Goita SF, Konaté L, Mounkoro K, Sarr MD, Seck AF, Toé L, Tourée S, and Remme JHF (2009). Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. *PLoS Negl Trop Dis* 3.7, e497. DOI: 10.1371/journal.pntd.0000497 (cit. on pp. 13, 23, 79, 81, 82, 113, 114, 130, 141, 143).

Dourmishev AL, Dourmishev LA, and Schwartz RA (2005). Ivermectin: pharmacology and application in dermatology. *Int J*

Dermatol 44.12, 981–988. DOI: 10.1111/j.1365-4632.2004.02253.x (cit. on pp. 95, 102).

Duerr HP, Dietz K, Buttner DW, and Schulz-Key H (2001). A stochastic model for the aggregation of *Onchocerca volvulus* in nodules. *Parasitology* 123.Pt 2, 193–201 (cit. on p. 8).

Duerr HP, Raddatz G, and Eichner M (2008). Diagnostic value of nodule palpation in onchocerciasis. *Trans R Soc Trop Med Hyg* 102.2, 148–154. DOI: 10.1016/j.trstmh.2007.10.009 (cit. on p. 30).

Duerr HP, Raddatz G, and Eichner M (2011). Control of onchocerciasis in Africa: threshold shifts, breakpoints and rules for elimination. *Int J Parasitol* 41.5, 581–589. DOI: 10.1016/j.ijpara.2010.12.009 (cit. on pp. 17, 37).

Duke BO (1968). The effects of drugs on *Onchocerca volvulus*. 1. Methods of assessment, population dynamics of the parasite and the effects of diethylcarbamazine. *Bull World Health Organ* 39.2, 137–146 (cit. on p. 2).

Duke BO (1980). Observations on *Onchocerca volvulus* in experimentally infected chimpanzees. *Tropenmed Parasitol* 31.1, 41–54 (cit. on p. 2).

Duke BO (1990). An improved method of examining adult *Onchocerca volvulus* worms. *Trop Med Parasitol* 41.1, 25–28 (cit. on p. 8).

Duke BO (1993). The population dynamics of *Onchocerca volvulus* in the human host. *Trop Med Parasitol* 44.2, 61–68 (cit. on pp. 2, 43, 65).

Duke BOL (2005). Evidence for macrofilaricidal activity of ivermectin against female *Onchocerca volvulus*: further analysis of a clinical trial in the Republic of Cameroon indicating two distinct killing mechanisms. *Parasitology* 130.Pt 4, 447–453 (cit. on p. 9).

Duke BO, Moore PJ, and De León JR (1967). Onchocerca-simulium complexes. V. The intake and subsequent fate of microfilariae of a Guatemalan strain of *Onchocerca volvulus* in forest and Sudan-savanna forms of West African *Simulium damnosum*. *Ann Trop Med Parasitol* 61.3, 332–337 (cit. on p. 2).

Duke BO, Pacqué MC, Muñoz B, Greene BM, and Taylor HR (1991a). Viability of adult *Onchocerca volvulus* after six 2-weekly

doses of ivermectin. *Bull World Health Organ* 69.2, 163–168 (cit. on pp. 116, 119).

Duke BO, Zea-Flores G, Castro J, Cupp EW, and Munoz B (1991b). Comparison of the effects of a single dose and of four six-monthly doses of ivermectin on adult *Onchocerca volvulus*. *Am J Trop Med Hyg* 45.1, 132–137 (cit. on pp. 116, 119, 130).

Duke BO, Zea-Flores G, Castro J, Cupp EW, and Munoz B (1992). Effects of three-month doses of ivermectin on adult *Onchocerca volvulus*. *Am J Trop Med Hyg* 46.2, 189–194 (cit. on pp. 116, 119, 130).

Duke BO, Zea-Flores G, Castro J, Cupp EW, and Muñoz B (1990). Effects of multiple monthly doses of ivermectin on adult *Onchocerca volvulus*. *Am J Trop Med Hyg* 43.6, 657–664 (cit. on pp. 116, 119).

Dunyo SK, Nkrumah FK, and Simonsen PE (2000). A randomized double-blind placebo-controlled field trial of ivermectin and albendazole alone and in combination for the treatment of lymphatic filariasis in Ghana. *Trans R Soc Trop Med Hyg* 94.2, 205–211 (cit. on p. 102).

Ejere H, Schwartz E, and Wormald R (2001). Ivermectin for onchocercal eye disease (river blindness). *Cochrane Database Syst Rev* 1, CD002219. DOI: 10.1002/14651858.CD002219 (cit. on p. 172).

Elkins DB, Haswell-Elkins M, and Anderson RM (1988). The importance of host age and sex to patterns of reinfection with Ascaris lumbricoides following mass anthelmintic treatment in a South Indian fishing community. *Parasitology* 96 (Pt 1), 171–184 (cit. on p. 100).

Eng JKL, Blackhall WJ, Osei-Atweneboana MY, Bourguinat C, Galazzo D, Beech RN, Unnasch TR, Awadzi K, Lubega GW, and Prichard RK (2006). Ivermectin selection on beta-tubulin: evidence in *Onchocerca volvulus* and Haemonchus contortus. *Mol Biochem Parasitol* 150.2, 229–235. DOI: 10.1016/j.molbiopara.2006.08.007 (cit. on p. 149).

Eng JKL and Prichard RK (2005). A comparison of genetic polymorphism in populations of *Onchocerca volvulus* from untreated- and ivermectin-treated patients. *Mol Biochem Parasitol* 142.2,

193–202. DOI: 10.1016/j.molbiopara.2005.01.021 (cit. on p. 149).

Enk CD (2006). Onchocerciasis–river blindness. *Clin Dermatol* 24.3, 176–180. DOI: 10.1016/j.clindermatol.2005.11.008 (cit. on p. 43).

Enyong P, Traoré S, Demanou M, Esum M, Fobi G, Noma M, Kayembé D, and Sékétéli A (2006). [African Programme for Onchocerdasis Control (APOC): *Onchocerca Simulium squamosum* in two regions in the Republic of Cameroon]. *Bull Soc Pathol Exot* 99.4, 272–277 (cit. on p. 45).

Feldmeier H (2009). [Tungiasis and cutaneous larva migrans: unpleasant travel souvenirs]. *Med Monatsschr Pharm* 32.12, 440–444 (cit. on p. 102).

Feldmeier H and Heukelbach J (2009). Epidermal parasitic skin diseases: a neglected category of poverty-associated plagues. *Bull World Health Organ* 87.2, 152–159 (cit. on pp. 95, 98, 102).

Filipe JAN, Boussinesq M, Renz A, Collins RC, Vivas-Martinez S, Grillet M.-E, Little MP, and Basáñez M.-G (2005). Human infection patterns and heterogeneous exposure in river blindness. *Proc Natl Acad Sci U S A* 102.42, 15265–15270. DOI: 10.1073/pnas.0502659102 (cit. on pp. 17, 37, 146).

Fischer P, Kipp W, Bamuhiga J, Binta-Kahwa J, Kiefer A, and Büttner DW (1993). Parasitological and clinical characterization of *Simulium neavei*-transmitted onchocerciasis in western Uganda. *Trop Med Parasitol* 44.4, 311–321 (cit. on pp. 8, 25–27, 30).

Flanagan W, McIntosh CN, Le Petit C, and Berthelot J.-M (2006). Deriving utility scores for co-morbid conditions: a test of the multiplicative model for combining individual condition scores. *Popul Health Metr* 4, 13. DOI: 10.1186/1478-7954-4-13 (cit. on p. 59).

Freedman DO, Zierdt WS, Lujan A, and Nutman TB (1989). The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis* 159.6, 1151–1153 (cit. on pp. 100, 101).

Gardon J, Gardon-Wendel N, Demanga-Ngangue, Kamgno J, Chippaux JP, and Boussinesq M (1997). Serious reactions after mass treatment of onchocerciasis with ivermectin in an area

endemic for *Loa loa* infection. *Lancet* 350.9070, 18–22. DOI: 10.1016/S0140-6736(96)11094-1 (cit. on pp. 9, 148).

Gardon J, Boussinesq M, Kamgno J, Gardon-Wendel N, Demanga-Ngangue, and Duke BOL (2002). Effects of standard and high doses of ivermectin on adult worms of *Onchocerca volvulus*: a randomised controlled trial. *Lancet* 360.9328, 203–210. DOI: 10.1016/S0140-6736(02)09456-4 (cit. on pp. 9, 76, 116, 119).

Gelman A (2006). Prior distributions for variance parameters in hierarchical models. *Bayesian Analysis* 1, 1–19. DOI: 10.1214/06-BA117A (cit. on p. 156).

Gelman A and Rubin DB (1992). Inference from Iterative Simulation Using Multiple Sequences. *Statistical Science* 7.4, 457–472 (cit. on p. 158).

Geweke J (1991). Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments. *Bayesian Statistics*. Ed. by J Bernado, J Berger, A Dawid, and A Smith. Clarendon Press (cit. on p. 158).

Gilmore SJ (2011). Control strategies for endemic childhood scabies. *PLoS One* 6.1, e15990. DOI: 10.1371/journal.pone.0015990 (cit. on p. 102).

Goldman AS, Guisinger VH, Aikins M, Amarillo MLE, Belizario VY, Garshong B, Gyapong J, Kabali C, Kamal HA, Kanjilal S, Kyelem D, Lizardo J, Malecela M, Mubyazi G, Nitièma PA, Ramzy RMR, Streit TG, Wallace A, Brady MA, Rheingans R, Ottesen EA, and Haddix AC (2007). National mass drug administration costs for lymphatic filariasis elimination. *PLoS Negl Trop Dis* 1.1, e67. DOI: 10.1371/journal.pntd.0000067 (cit. on p. 81).

González-Muñoz M, Gárate T, Puente S, Subirats M, and Moneo I (1999). Induction of histamine release in parasitized individuals by somatic and cuticular antigens from *Onchocerca volvulus*. *Am J Trop Med Hyg* 60.6, 974–979 (cit. on p. 57).

Gopal H, Hassan HK, Rodríguez-Pérez MA, Toé LD, Lustigman S, and Unnasch TR (2012). Oligonucleotide Based Magnetic Bead Capture of *Onchocerca volvulus* DNA for PCR Pool Screening of Vector Black Flies. *PLoS Negl Trop Dis* 6.6, e1712. DOI: 10.1371/journal.pntd.0001712 (cit. on pp. 8, 148).

Green MJ, Medley GF, and Browne WJ (2009). Use of posterior predictive assessments to evaluate model fit in multilevel logistic regression. *Vet Res* 40.4, 30. DOI: 10.1051/vetres/2009013 (cit. on p. 31).

Guderian RH (1988). Effects of nodulectomy in onchocerciasis in Ecuador. *Trop Med Parasitol* 39 Suppl 4, 356–357 (cit. on p. 9).

Guderian RH, Proaño R, Beck B, and Mackenzie CD (1987). The reduction in microfilariae loads in the skin and eye after nodulectomy in Ecuadorian onchocerciasis. *Trop Med Parasitol* 38.4, 275–278 (cit. on p. 9).

Gutman J, Emukah E, Okpala N, Okoro C, Obasi A, Miri ES, and Richards Jr FO (2010). Effects of annual mass treatment with ivermectin for onchocerciasis on the prevalence of intestinal helminths. *Am J Trop Med Hyg* 83.3, 534–541. DOI: 10.4269/ajtmh.2010.10-0033 (cit. on pp. 95, 100, 101, 107).

Haagsma JA, van Beeck EF, Polinder S, Toet H, Panneman M, and Bonsel GJ (2011). The effect of comorbidity on health-related quality of life for injury patients in the first year following injury: comparison of three comorbidity adjustment approaches. *Popul Health Metr* 9, 10. DOI: 10.1186/1478-7954-9-10 (cit. on p. 59).

Habbema JDF, van Oortmarssen GJ, and Plaisier AP (1996). The ONCHOSIM model and its use in decision support for river blindness control. *Models for Infectious Human Diseases - Their structure and relation to data.* Ed. by V Isham and G Medley. Cambridge University Press, 360–380. DOI: http://dx.doi.org/10.1017/CBO9780511662935.052 (cit. on pp. 17, 68, 69, 114, 115, 141).

Hengge UR, Currie BJ, Jäger G, Lupi O, and Schwartz RA (2006). Scabies: a ubiquitous neglected skin disease. *Lancet Infect Dis* 6.12, 769–779. DOI: 10.1016/S1473-3099(06)70654-5 (cit. on p. 102).

Henry MC and Maertens K (1990). The onchocerciasis focus at Kinsuka/Kinshasa (Republic of Zaire) in 1985. II. Parasitological and clinical aspects. *Ann Trop Med Parasitol* 84.5, 493–502 (cit. on p. 176).

Herder S (1994). „The genetic variation of *Onchocerca volvulus* (Leukart, 1893) Relation with the epidemiological profile of onchocerciasis [Variabilité génétique d'*Onchocerca volvulus* (Leukart, 1893). Relations avec les faciès épidémiologiques de l'onchocercose]". Université de Monpellier II (cit. on p. 36).

Herder S, Bellec C, Meredith SE, and Cuny G (1994). Genomic fingerprinting of *Onchocerca* species using random amplified polymorphic DNA. *Trop Med Parasitol* 45.3, 199–202 (cit. on p. 36).

Heukelbach J, Winter B, Wilcke T, Muehlen M, Albrecht S, de Oliveira FAS, Kerr-Pontes LRS, Liesenfeld O, and Feldmeier H (2004). Selective mass treatment with ivermectin to control intestinal helminthiases and parasitic skin diseases in a severely affected population. *Bull World Health Organ* 82.8, 563–571. DOI: /S0042-96862004000800005 (cit. on p. 102).

Hoerauf A (2008). Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis. *Curr Opin Infect Dis* 21.6, 673–681. DOI: 10.1097/QCO.0b013e328315cde7 (cit. on pp. 10, 148).

Hoerauf A, Kruse S, Brattig NW, Heinzmann A, Mueller-Myhsok B, and Deichmann KA (2002). The variant Arg110Gln of human IL-13 is associated with an immunologically hyper-reactive form of onchocerciasis (sowda). *Microbes Infect* 4.1, 37–42 (cit. on p. 43).

Hoerauf A, Specht S, Marfo-Debrekyei Y, Büttner M, Debrah AY, Mand S, Batsa L, Brattig N, Konadu P, Bandi C, Fimmers R, Adjei O, and Büttner DW (2009). Efficacy of 5-week doxycycline treatment on adult *Onchocerca volvulus*. *Parasitol Res* 104.2, 437–447. DOI: 10.1007/s00436-008-1217-8 (cit. on p. 148).

Hopkins DR, Richards Jr FO, Ruiz-Tiben E, Emerson P, and Withers Jr PC (2008). Dracunculiasis, onchocerciasis, schistosomiasis, and trachoma. *Ann N Y Acad Sci* 1136, 45–52. DOI: 10.1196/annals.1425.015 (cit. on p. 150).

Hotez PJ, Bottazzi ME, Franco-Paredes C, Ault SK, and Periago MR (2008). The neglected tropical diseases of Latin America and the Caribbean: a review of disease burden and distribution and a roadmap for control and elimination. *PLoS Negl Trop*

Dis 2.9, e300. DOI: 10.1371/journal.pntd.0000300 (cit. on p. 150).

Hotez PJ and Kamath A (2009). Neglected tropical diseases in sub-saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Negl Trop Dis* 3.8, e412. DOI: 10.1371/journal.pntd.0000412 (cit. on pp. 95, 108).

Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, and Savioli L (2007). Control of neglected tropical diseases. *N Engl J Med* 357.10, 1018–1027. DOI: 10.1056/NEJMra064142 (cit. on pp. 100, 101).

Kabatereine NB, Fleming FM, Nyandindi U, Mwanza JCL, and Blair L (2006). The control of schistosomiasis and soil-transmitted helminths in East Africa. *Trends Parasitol* 22.7, 332–339. DOI: 10.1016/j.pt.2006.05.001 (cit. on p. 150).

Kaiser C, Pion S, and Boussinesq M (2009). Head nodding syndrome and river blindness: a parasitologic perspective. *Epilepsia* 50.10, 2325–2326. DOI: 10.1111/j.1528-1167.2009.02280.x (cit. on p. 6).

Kar SK, Mania J, and Patnaik S (1994). The use of ivermectin for scabies. *Natl Med J India* 7.1, 15–16 (cit. on p. 102).

Katabarwa MN, Eyamba A, Chouaibou M, Enyong P, Kuété T, Yaya S, Yougouda A, Baldiagaï J, Madi K, Andze GO, and Richards F (2010). Does onchocerciasis transmission take place in hypoendemic areas? A study from the North Region of Cameroon. *Trop Med Int Health* 15.5, 645–652. DOI: 10.1111/j.1365-3156.2010.02501.x (cit. on p. 145).

Katholi CR and Unnasch TR (2006). Important experimental parameters for determining infection rates in arthropod vectors using pool screening approaches. *Am J Trop Med Hyg* 74.5, 779–785 (cit. on pp. 8, 148).

Kayembe DL, Kasonga DL, Kayembe PK, Mwanza J.-CK, and Boussinesq M (2003). Profile of eye lesions and vision loss: a cross-sectional study in Lusambo, a forest-savanna area hyperendemic for onchocerciasis in the Democratic Republic of Congo. *Trop Med Int Health* 8.1, 83–89 (cit. on p. 176).

Kim A (1997). *Health and Labor Productivity: the economic impact of onchocercal skin disease*. Tech. rep. The World Bank (cit. on pp. 11, 76, 82).

King CH and Bertino A.-M (2008). Asymmetries of poverty: why global burden of disease valuations underestimate the burden of neglected tropical diseases. *PLoS Negl Trop Dis* 2.3, e209. DOI: 10.1371/journal.pntd.0000209 (cit. on p. 87).

Kipp W, Burnham G, Bamuhiiga J, and Leichsenring M (1996). The Nakalanga syndrome in Kabarole District, Western Uganda. *Am J Trop Med Hyg* 54.1, 80–83 (cit. on p. 6).

Kipp W and Bamhuhiiga J (2002). Validity of nodule palpation in a *Simulium neavei*-transmitted onchocerciasis area in Uganda. *Am J Trop Med Hyg* 67.1, 128–131 (cit. on p. 24).

Kirkwood B, Smith P, Marshall T, and Prost A (1983). Relationships between mortality, visual acuity and microfilarial load in the area of the Onchocerciasis Control Programme. *Trans R Soc Trop Med Hyg* 77.6, 862–868 (cit. on p. 10).

Kläger SL, Whitworth JA, and Downham MD (1996). Viability and fertility of adult *Onchocerca volvulus* after 6 years of treatment with ivermectin. *Trop Med Int Health* 1.5, 581–589 (cit. on pp. 116, 119).

Kläger S, Whitworth JA, Post RJ, Chavasse DC, and Downham MD (1993). How long do the effects of ivermectin on adult *Onchocerca volvulus* persist? *Trop Med Parasitol* 44.4, 305–310 (cit. on pp. 116, 119).

Kudzi W, Dodoo ANO, and Mills JJ (2010). Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes in a Ghanaian population: a plausible explanation for altered metabolism of ivermectin in humans? *BMC Med Genet* 11, 111. DOI: 10.1186/1471-2350-11-111 (cit. on p. 149).

Lawrence G, Leafasia J, Sheridan J, Hills S, Wate J, Wate C, Montgomery J, Pandeya N, and Purdie D (2005). Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. *Bull World Health Organ* 83.1, 34–42. DOI: /S0042-96862005000100012 (cit. on p. 102).

Le Berre R, Balay G, Brengues J, and Coz J (1964). Biology and ecology of the female of *Simulium damnosum* Theobald, 1903,

as a function of the bioclimatic zones of West Africa. Influence on the epidemiology of onchocerciasis. [Biologie et l'écologie de la femelle de *Simulium damnosum* Theobald, 1903, en fonction des zones bioclimatiques d'Afrique Occidentale. Influence sur l'épidémiologie de l'onchocercose]. *Bull World Health Organ* 31, 843–855 (cit. on p. 35).

Little MP, Breitling LP, Basáñez M.-G, Alley ES, and Boatin BA (2004a). Association between microfilarial load and excess mortality in onchocerciasis: an epidemiological study. *Lancet* 363.9420, 1514–1521. DOI: 10.1016/S0140-6736(04)16151-5 (cit. on pp. 10, 76, 145).

Little MP, Basanez M.-G, Breitling LP, Boatin BA, and Alley ES (2004b). Incidence of blindness during the Onchocerciasis control programme in western Africa, 1971-2002. *J Infect Dis* 189.10, 1932–1941. DOI: 10.1086/383326 (cit. on p. 43).

London School of Hygiene and Tropical Medicine (2009). The Global Atlas of Helminth Infections (cit. on pp. 95, 98, 103).

Macé JM, Boussinesq M, Ngoumou P, Enyegue Oye J, Koéranga A, and Godin C (1997). Country-wide rapid epidemiological mapping of onchocerciasis (REMO) in Cameroon. *Ann Trop Med Parasitol* 91.4, 379–391 (cit. on p. 45).

Mackenzie CD (2007). Efficacy of ivermectin against *Onchocerca volvulus* in Ghana. *Lancet* 370.9593, 1123, 1123, author reply 1125. DOI: 10.1016/S0140-6736(07)61502-5 (cit. on p. 149).

Mackenzie CD and Geary TG (2011). Flubendazole: a candidate macrofilaricide for lymphatic filariasis and onchocerciasis field programs. *Expert Rev Anti Infect Ther* 9.5, 497–501. DOI: 10.1586/eri.11.30 (cit. on pp. 10, 148).

Mackenzie CD, Homeida MM, Hopkins AD, and Lawrence JC (2012). Elimination of onchocerciasis from Africa: possible? *Trends Parasitol* 28.1, 16–22. DOI: 10.1016/j.pt.2011.10.003 (cit. on pp. 23, 82).

Makunde WH, Salum FM, Massaga JJ, and Alilio MS (2000). Clinical and parasitological aspects of itching caused by onchocerciasis in Morogoro, Tanzania. *Ann Trop Med Parasitol* 94.8, 793–799 (cit. on p. 57).

Marshall EC and Spiegelhalter DJ (2003). Approximate cross-validatory predictive checks in disease mapping models. *Stat Med* 22.10, 1649–1660. DOI: 10.1002/sim.1403 (cit. on p. 31).

Marti H, Haji HJ, Savioli L, Chwaya HM, Mgeni AF, Ameir JS, and Hatz C (1996). A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg* 55.5, 477–481 (cit. on p. 101).

Mathers C, Vos T, and Stevenson C (1999). *The burden of disease and injury in Australia*. Cat. no. PHE 17. AIHW, p. 273. ISRN: 978 1 74024 019 2 (cit. on p. 50).

Mathers CD, Ezzati M, and Lopez AD (2007). Measuring the burden of neglected tropical diseases: the global burden of disease framework. *PLoS Negl Trop Dis* 1.2, e114. DOI: 10.1371/journal.pntd.0000114 (cit. on pp. 11, 49, 59, 60).

Mathers CD, Iburg KM, and Begg S (2006). Adjusting for dependent comorbidity in the calculation of healthy life expectancy. *Popul Health Metr* 4, 4. DOI: 10.1186/1478-7954-4-4 (cit. on pp. 50, 59).

McKechnie NM, Braun G, Connor V, Kläger S, Taylor DW, Alexander RA, and Gilbert CE (1993). Immunologic cross-reactivity in the pathogenesis of ocular onchocerciasis. *Invest Ophthalmol Vis Sci* 34.10, 2888–2902 (cit. on p. 57).

McKechnie NM, Gürr W, Yamada H, Copland D, and Braun G (2002). Antigenic mimicry: *Onchocerca volvulus* antigen-specific T cells and ocular inflammation. *Invest Ophthalmol Vis Sci* 43.2, 411–418 (cit. on p. 57).

McMahon JE, Sowa SI, Maude GH, and Kirkwood BR (1988). Onchocerciasis in Sierra Leone 2: A comparison of forest and savanna villages. *Trans R Soc Trop Med Hyg* 82.4, 595–600 (cit. on pp. 4, 43).

Medley GF, Guyatt HL, and Bundy DA (1993). A quantitative framework for evaluating the effect of community treatment on the morbidity due to ascariasis. *Parasitology* 106 (Pt 2), 211–221 (cit. on p. 108).

Meinking TL, Taplin D, Hermida JL, Pardo R, and Kerdel FA (1995). The treatment of scabies with ivermectin. *N Engl J Med* 333.1, 26–30. DOI: 10.1056/NEJM199507063330105 (cit. on p. 102).

Meyer CG, Gallin M, Erttmann KD, Brattig N, Schnittger L, Gelhaus A, Tannich E, Begovich AB, Erlich HA, and Horstmann RD (1994). HLA-D alleles associated with generalized disease, localized disease, and putative immunity in *Onchocerca volvulus* infection. *Proc Natl Acad Sci U S A* 91.16, 7515–7519 (cit. on p. 43).

Migliani R, Louis J, Auduge A, Trebucq A, and Gelas H (1993). Evaluation of visual impairment and blindness in Cameroon. A survey in a forest area. [Évaluation de la malvoyance et des cécités au Cameroun. Enquête en milieu rural forestier]. *Cahier Santé* 3, 17–23 (cit. on p. 36).

Molyneux DH (2006). Control of human parasitic diseases: Context and overview. *Adv Parasitol* 61, 1–45. DOI: 10.1016/S0065-308X(05)61001-9 (cit. on p. 150).

Moncayo AL, Vaca M, Amorim L, Rodriguez A, Erazo S, Oviedo G, Quinzo I, Padilla M, Chico M, Lovato R, Gomez E, Barreto ML, and Cooper PJ (2008). Impact of long-term treatment with ivermectin on the prevalence and intensity of soil-transmitted helminth infections. *PLoS Negl Trop Dis* 2.9, e293. DOI: 10.1371/journal.pntd.0000293 (cit. on pp. 100, 101).

Mont D (2007). Measuring health and disability. *Lancet* 369.9573, 1658–1663. DOI: 10.1016/S0140-6736(07)60752-1 (cit. on p. 87).

Montresor A, Cong DT, Sinuon M, Tsuyuoka R, Chanthavisouk C, Strandgaard H, Velayudhan R, Capuano CM, Le Anh T, and Tee Dató AS (2008). Large-scale preventive chemotherapy for the control of helminth infection in Western Pacific countries: six years later. *PLoS Negl Trop Dis* 2.8, e278. DOI: 10.1371/journal.pntd.0000278 (cit. on p. 150).

Moreau JP, Prost A, and Prod'hon J (1978). [An attempt to normalize the methodology of clinico parasitologic surveys of onchocerciasis in West-Africa (author's transl)]. *Med Trop (Mars)* 38.1, 43–51 (cit. on p. 6).

Murdoch ME (1992). The skin and the immune response in onchocerciasis. *Trop Doct* 22 Suppl 1, 44–55, 61–2 (cit. on pp. 5, 6).

Murdoch ME, Asuzu MC, Hagan M, Makunde WH, Ngoumou P, Ogbuagu KF, Okello D, Ozoh G, and Remme J (2002). Onchocerciasis: the clinical and epidemiological burden of skin disease in Africa. *Ann Trop Med Parasitol* 96.3, 283–296. DOI: 10.1179/000349802125000826 (cit. on pp. 4, 10, 57, 76, 88, 90, 178–180).

Murdoch ME, Hay RJ, Mackenzie CD, Williams JF, Ghalib HW, Cousens S, Abiose A, and Jones BR (1993). A clinical classification and grading system of the cutaneous changes in onchocerciasis. *Br J Dermatol* 129.3, 260–269 (cit. on pp. 4, 46, 59, 138).

Murdoch ME, Payton A, Abiose A, Thomson W, Panicker VK, Dyer PA, Jones BR, Maizels RM, and Ollier WE (1997). HLA-DQ alleles associate with cutaneous features of onchocerciasis. The Kaduna-London-Manchester Collaboration for Research on Onchocerciasis. *Hum Immunol* 55.1, 46–52 (cit. on p. 43).

Murdoch M (2008). Skin signs of onchocerciasis. *J Comm Dermatol* 5.8, 16–20 (cit. on p. 5).

Murdoch ME (2010). Onchodermatitis. *Curr Opin Infect Dis* 23.2, 124–131. DOI: 10.1097/QCO.0b013e328336a256 (cit. on pp. 4, 10, 59, 90).

Murray CJL and Lopez AD (1996). Global Health Statistics. Cambridge: Harvard University Press (cit. on pp. 12, 50).

Murray CJ and Lopez AD (2000). Progress and directions in refining the global burden of disease approach: a response to Williams. *Health Econ* 9.1, 69–82 (cit. on pp. 44, 50, 137).

Murray CJL et al. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380.9859, 2197–2223. DOI: 10.1016/S0140-6736(12)61689-4 (cit. on pp. 95–97, 103, 104, 108, 138, 140).

Mwinzi PNM, Montgomery SP, Owaga CO, Mwanje M, Muok EM, Ayisi JG, Laserson KF, Muchiri EM, Secor WE, and Karanja DMS (2012). Integrated community-directed intervention for

schistosomiasis and soil transmitted helminths in western Kenya - a pilot study. *Parasit Vectors* 5, 182. DOI: 10.1186/1756-3305-5-182 (cit. on p. 132).

Naquira C, Jimenez G, Guerra JG, Bernal R, Nalin DR, Neu D, and Aziz M (1989). Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 40.3, 304–309 (cit. on pp. 100, 101).

Newell ED (1997). Comparison of the use of skin scarification and skin biopsies to determine the prevalence and intensity of *Onchocerca volvulus* infection. *Ann Trop Med Parasitol* 91.6, 633–642 (cit. on p. 7).

Ngoumou P and Walsh J (1993). *A Manual for Rapid Epidemiological Mapping of Onchocerciasis*. TDR/TDE/ONCHO/93.4. UNDP/World Bank/WHO (cit. on pp. 7, 8, 14, 24, 27, 31, 37, 166, 168).

Noma M, Nwoke BEB, Nutall I, Tambala PA, Enyong P, Namsenmo A, Remme J, Amazigo UV, Kale OO, and Sékétéli A (2002). Rapid epidemiological mapping of onchocerciasis (REMO): its application by the African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol* 96 Suppl 1, S29–S39 (cit. on pp. 8, 14, 24, 31, 65, 103, 166, 168).

Nontasut P, Muennoo C, Sa-nguankiat S, Fongsri S, and Vichit A (2005). Prevalence of strongyloides in Northern Thailand and treatment with ivermectin vs albendazole. *Southeast Asian J Trop Med Public Health* 36.2, 442–444 (cit. on p. 101).

O'Brien SM and Dunson DB (2004). Bayesian multivariate logistic regression. *Biometrics* 60.3, 739–746. DOI: 10.1111/j.0006-341X.2004.00224.x (cit. on p. 154).

Olsen A (2007). Efficacy and safety of drug combinations in the treatment of schistosomiasis, soil-transmitted helminthiasis, lymphatic filariasis and onchocerciasis. *Trans R Soc Trop Med Hyg* 101.8, 747–758. DOI: 10.1016/j.trstmh.2007.03.006 (cit. on p. 101).

Onwujekwe O, Chima R, Shu E, and Okonkwo P (2002). Community-directed treatment with ivermectin in two Nigerian communities: an analysis of first year start-up processes, costs and consequences. *Health Policy* 62.1, 31–51 (cit. on p. 81).

Osei-Atweneboana MY, Awadzi K, Attah SK, Boakye DA, Gyapong JO, and Prichard RK (2011). Phenotypic evidence of emerging ivermectin resistance in *Onchocerca volvulus*. *PLoS Negl Trop Dis* 5.3, e998. DOI: 10.1371/journal.pntd.0000998 (cit. on p. 149).

Osei-Atweneboana MY, Eng JKL, Boakye DA, Gyapong JO, and Prichard RK (2007). Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. *Lancet* 369.9578, 2021–2029. DOI: 10.1016/S0140-6736(07)60942-8 (cit. on p. 149).

Ottesen EA, Hooper PJ, Bradley M, and Biswas G (2008). The global programme to eliminate lymphatic filariasis: health impact after 8 years. *PLoS Negl Trop Dis* 2.10, e317. DOI: 10.1371/journal.pntd.0000317 (cit. on pp. 95, 108).

Ovaskainen O, Hottola J, and Siitonen J (2010). Modeling species co-occurrence by multivariate logistic regression generates new hypotheses on fungal interactions. *Ecology* 91, 2514–2521. DOI: 10.1890/10-0173.1 (cit. on p. 154).

Ozoh GA, Murdoch ME, Bissek A.-C, Hagan M, Ogbuagu K, Shamad M, Braide EI, Boussinesq M, Noma MM, Murdoch IE, Sékétéli A, and Amazigo UV (2011). The African Programme for Onchocerciasis Control: impact on onchocercal skin disease. *Trop Med Int Health* 16.7, 875–883. DOI: 10.1111/j.1365-3156.2011.02783.x (cit. on pp. 14, 46, 76, 79).

Ozoh G, Boussinesq M, Bissek A.-CZ.-K, Kobangue L, Kombila M, Mbina J.-RM, Enyong P, Noma M, Sékétéli A, and Fobi G (2007). Evaluation of the diethylcarbamazine patch to evaluate onchocerciasis endemicity in Central Africa. *Trop Med Int Health* 12.1, 123–129. DOI: 10.1111/j.1365-3156.2006.01750.x (cit. on p. 148).

Padmasiri EA, Montresor A, Biswas G, and de Silva NR (2006). Controlling lymphatic filariasis and soil-transmitted helminthiasis together in South Asia: opportunities and challenges. *Trans R Soc Trop Med Hyg* 100.9, 807–810. DOI: 10.1016/j.trstmh.2005.12.001 (cit. on p. 150).

Pearlman E and Gillette-Ferguson I (2007). *Onchocerca volvulus*, Wolbachia and river blindness. *Chem Immunol Allergy* 92, 254–265. DOI: 10.1159/000099276 (cit. on p. 2).

Peters W and Pasvol G (2007). Atlas of Tropical Medicine and Parasitology. Elsevier Mosby, 128. ISBN: 9780323043649 (cit. on p. 7).

Pion SDS, Kamgno J, Demanga-Ngangue, and Boussinesq M (2002). Excess mortality associated with blindness in the onchocerciasis focus of the Mbam Valley, Cameroon. *Ann Trop Med Parasitol* 96.2, 181–189. DOI: 10.1179/000349802125000718 (cit. on p. 10).

Pion SDS and Boussinesq M (2012). Significant association between epilepsy and presence of onchocercal nodules: case-control study in Cameroon. *Am J Trop Med Hyg* 86.3, 557, author reply 558. DOI: 10.4269/ajtmh.2012.11-0603a (cit. on p. 6).

Pion SDS, Grout L, Kamgno J, Nana-Djeunga H, and Boussinesq M (2011). Individual host factors associated with *Onchocerca volvulus* microfilarial densities 15, 80 and 180 days after a first dose of ivermectin. *Acta Trop* 120 Suppl 1, S91–S99. DOI: 10.1016/j.actatropica.2010.05.004 (cit. on p. 149).

Pion SDS, Kaiser C, Boutros-Toni F, Cournil A, Taylor MM, Meredith SEO, Stufe A, Bertocchi I, Kipp W, Preux P.-M, and Boussinesq M (2009). Epilepsy in onchocerciasis endemic areas: systematic review and meta-analysis of population-based surveys. *PLoS Negl Trop Dis* 3.6, e461. DOI: 10.1371/journal.pntd.0000461 (cit. on pp. 6, 76).

Plaisier AP, Alley ES, Boatin BA, van Oortmarssen GJ, Remme H, de Vlas SJ, Bonneux L, and Habbema JD (1995). Irreversible effects of ivermectin on adult parasites in onchocerciasis patients in the Onchocerciasis Control Programme in West Africa. *J Infect Dis* 172.1, 204–210 (cit. on pp. 9, 18, 65, 68, 79, 80, 114, 116, 141, 184).

Plaisier AP, Alley ES, van Oortmarssen GJ, Boatin BA, and Habbema JD (1997). Required duration of combined annual ivermectin treatment and vector control in the Onchocerciasis Control Programme in west Africa. *Bull World Health Organ* 75.3, 237–245 (cit. on pp. 18, 23, 37, 66, 68, 79, 114, 116, 169, 174).

Plaisier AP, Cao WC, van Oortmarssen GJ, and Habbema JD (1999). Efficacy of ivermectin in the treatment of Wuchereria bancrofti infection: a model-based analysis of trial results. *Parasitology* 119 (Pt 4), 385–394 (cit. on p. 102).

Plaisier AP, van Oortmarssen GJ, Habbema JD, Remme J, and Alley ES (1990). ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. *Comput Methods Programs Biomed* 31.1, 43–56 (cit. on pp. 17, 37, 66, 68, 69, 114, 141, 169, 172).

Plaisier AP, van Oortmarssen GJ, Remme J, Alley ES, and Habbema JD (1991a). The risk and dynamics of onchocerciasis recrudescence after cessation of vector control. *Bull World Health Organ* 69.2, 169–178 (cit. on pp. 12, 18, 79, 141).

Plaisier AP, van Oortmarssen GJ, Remme J, and Habbema JD (1991b). The reproductive lifespan of *Onchocerca volvulus* in West African savanna. *Acta Trop* 48.4, 271–284 (cit. on pp. 2, 18, 79, 115, 141).

Poolman EM and Galvani AP (2006). Modeling targeted ivermectin treatment for controlling river blindness. *Am J Trop Med Hyg* 75.5, 921–927 (cit. on pp. 17, 37).

Prost A (1986). The burden of blindness in adult males in the savanna villages of West Africa exposed to onchocerciasis. *Trans R Soc Trop Med Hyg* 80.4, 525–527 (cit. on p. 10).

Prost A and Vaugelade J (1981). [Excess mortality among blind persons in the West African savannah zone]. *Bull World Health Organ* 59.5, 773–776 (cit. on p. 10).

Quillévéré D, Hougard JM, and Prud'hom JM (1990). [Study of the transmission of onchocerciasis in the surroundings of a refugee camp located in the savanna zone of Cameroon]. *Ann Soc Belg Med Trop* 70.3, 193–202 (cit. on pp. 25, 26).

R Core Team (2013). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing (cit. on p. 31).

Rees J and Murray CS (2005). Itching for progress. *Clin Exp Dermatol* 30.5, 471–473. DOI: 10.1111/j.1365-2230.2005.01852.x (cit. on p. 57).

Remme JHF (2004). *The Global Burden of Onchocerciasis in 1990*. Tech. rep. World Health Organization (cit. on pp. 12, 19, 24–26, 59, 136, 170, 171, 174–177).

Remme JHF, Feenstra P, Lever PR, Medici MC, Morel CM, Noma M, Ramalah KD, Richards F, Seketeli A, Schmunis G, Brakel WH van, and Vassal A (2006). „Tropical diseases targeted for elimination: chagas disease, lymphatic filariasis, onchocerciasis, and leprosy". *Disease Control Priorities in Developing Countries*. Ed. by DT Jamison, JG Breman, AR Measham, G Alleyne, M Claeson, D Evans, P Jha, A Mills, and P Musgrove. 2nd. The World Bank. Chap. 22 (cit. on pp. 12, 81).

Remme J, Ba O, Dadzie KY, and Karam M (1986). A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River basin area. *Bull World Health Organ* 64.5, 667–681 (cit. on p. 7).

Remme J, Dadzie KY, Rolland A, and Thylefors B (1989). Ocular onchocerciasis and intensity of infection in the community. I. West African savanna. *Trop Med Parasitol* 40.3, 340–347 (cit. on pp. 3, 4, 23, 25, 26, 37, 173).

Remme JHF, Amazigo U, Engels D, Barryson A, and Yameogo L (2007). Efficacy of ivermectin against *Onchocerca volvulus* in Ghana. *Lancet* 370.9593, 1123–4, 1123–4. DOI: 10.1016/S0140-6736(07)61503-7 (cit. on p. 149).

Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, and Mariotti SP (2004). Global data on visual impairment in the year 2002. *Bull World Health Organ* 82.11, 844–851. DOI: /S0042-96862004001100009 (cit. on pp. 176, 177).

Richard-Lenoble D, Kombila M, Rupp EA, Pappayliou ES, Gaxotte P, Nguiri C, and Aziz MA (1988). Ivermectin in loiasis and concomitant *O. volvulus* and M. perstans infections. *Am J Trop Med Hyg* 39.5, 480–483 (cit. on p. 100).

Richards Jr F, Eigege A, Pam D, Kal A, Lenhart A, Oneyka JOA, Jinadu MY, and Miri ES (2005). Mass ivermectin treatment for onchocerciasis: lack of evidence for collateral impact on transmis-

sion of *Wuchereria bancrofti* in areas of co-endemicity. *Filaria J* 4, 6. DOI: 10.1186/1475-2883-4-6 (cit. on p. 102).

Rodríguez-Pérez MA, Unnasch TR, and Real-Najarro O (2011). Assessment and monitoring of onchocerciasis in Latin America. *Adv Parasitol* 77, 175–226. DOI: 10.1016/B978-0-12-391429-3.00008-3 (cit. on p. 8).

Rothova A, van der Lelij A, Stilma JS, Wilson WR, and Barbe RF (1989). Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* 1.8652, 1439–1441 (cit. on p. 9).

Rubio de Krömer MT, Medina-De la Garza CE, and Brattig NW (1995). Differences in eosinophil and neutrophil chemotactic responses in sowda and generalized form of onchocerciasis. *Acta Trop* 60.1, 21–33 (cit. on p. 43).

Salomon JA, Vos T, and Murray CJL (2013). Disability weights for vision disorders in Global Burden of Disease study - Authors' reply. *Lancet* 381.9860, 23–24. DOI: 10.1016/S0140-6736(12)62131-X (cit. on p. 90).

Salomon JA et al. (2012). Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 380.9859, 2129–2143. DOI: 10.1016/S0140-6736(12)61680-8 (cit. on pp. 87, 88, 90, 136).

Santiago M and Leitão B (2009). Prevention of strongyloides hyperinfection syndrome: a rheumatological point of view. *Eur J Intern Med* 20.8, 744–748. DOI: 10.1016/j.ejim.2009.09.001 (cit. on p. 101).

Sauerbrey M (2008). The Onchocerciasis Elimination Program for the Americas (OEPA). *Ann Trop Med Parasitol* 102 Suppl 1, 25–29. DOI: 10.1179/136485908X337454 (cit. on pp. 16, 113).

Schulz-Key H (1988). The collagenase technique: how to isolate and examine adult *Onchocerca volvulus* for the evaluation of drug effects. *Trop Med Parasitol* 39 Suppl 4, 423–440 (cit. on p. 8).

Schulz-Key H and Albiez EJ (1977). Worm burden of onchocerca volvulus in a hyperendemic village of the rain-forest in West Africa. *Tropenmed Parasitol* 28.4, 431–438 (cit. on p. 2).

Sékétéli A, Adeoye G, Eyamba A, Nnoruka E, Drameh P, Amazigo UV, Noma M, Agboton F, Aholou Y, Kale OO, and Dadzie

KY (2002). The achievements and challenges of the African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol* 96 Suppl 1, S15–S28 (cit. on p. 13).

Semba RD, Murphy RP, Newland HS, Awadzi K, Greene BM, and Taylor HR (1990). Longitudinal study of lesions of the posterior segment in onchocerciasis. *Ophthalmology* 97.10, 1334–1341 (cit. on p. 3).

Shah M, Johns B, Abimiku A, and Walker DG (2011). Cost-effectiveness of new WHO recommendations for prevention of mother-to-child transmission of HIV in a resource-limited setting. *AIDS* 25.8, 1093–1102. DOI: 10.1097/QAD.0b013e32834670b9 (cit. on p. 81).

Shikiya K, Kinjo N, Uehara T, Uechi H, Ohshiro J, Arakaki T, Kinjo F, Saito A, Iju M, and Kobari K (1992). Efficacy of ivermectin against Strongyloides stercoralis in humans. *Intern Med* 31.3, 310–312 (cit. on p. 101).

Shikiya K, Uehara T, Uechi H, Ohshiro J, Arakaki T, Oyakawa T, Sakugawa H, Kinjo F, Saito A, and Asato R (1991). [Clinical study on ivermectin against Strongyloides stercoralis]. *Kansenshogaku Zasshi* 65.9, 1085–1090 (cit. on p. 101).

Southgate BA and Bryan JH (1992). Factors affecting transmission of Wuchereria bancrofti by anopheline mosquitoes. 4. Facilitation, limitation, proportionality and their epidemiological significance. *Trans R Soc Trop Med Hyg* 86.5, 523–530 (cit. on p. 142).

Specht S, Hoerauf A, Adjei O, Debrah A, and Büttner DW (2009). Newly acquired *Onchocerca volvulus* filariae after doxycycline treatment. *Parasitol Res* 106.1, 23–31. DOI: 10.1007/s00436-009-1624-5 (cit. on p. 148).

Spiegelhalter D, Best N, Carlin B, and Van der Linde A (2002). Bayesian measures of model complexity and fit. *J R Statist Soc B* 64, 583–639 (cit. on p. 31).

Stern MS and Joshpe G (1971). Strongyloides stercoralis autoinfection. *JAMA* 215.2, 297–298 (cit. on p. 101).

Stolk WA, de Vlas SJ, Borsboom GJJM, and Habbema JDF (2008). LYMFASIM, a simulation model for predicting the impact of lymphatic filariasis control: quantification for African villages.

Parasitology 135.13, 1583–1598. DOI: 10.1017/S0031182008000437 (cit. on p. 108).

Stolk WA, ten Bosch QA, de Vlas SJ, Fischer PU, Weil GJ, and Goldman AS (2013). Modeling the impact and costs of semi-annual mass drug administration for accelerated elimination of lymphatic filariasis. *PLoS Negl Trop Dis* 7.1, e1984. DOI: 10.1371/journal.pntd.0001984 (cit. on pp. 113, 132).

Subramanian S, Stolk WA, Ramaiah KD, Plaisier AP, Krishnamoorthy K, Van Oortmarssen GJ, Dominic Amalraj D, Habbema JDF, and Das PK (2004). The dynamics of Wuchereria bancrofti infection: a model-based analysis of longitudinal data from Pondicherry, India. *Parasitology* 128.Pt 5, 467–482 (cit. on pp. 142, 145).

Sule HM and Thacher TD (2007). Comparison of ivermectin and benzyl benzoate lotion for scabies in Nigerian patients. *Am J Trop Med Hyg* 76.2, 392–395 (cit. on p. 102).

Tamarozzi F, Tendongfor N, Enyong PA, Esum M, Faragher B, Wanji S, and Taylor MJ (2012). Long term impact of large scale community-directed delivery of doxycycline for the treatment of onchocerciasis. *Parasit Vectors* 5, 53. DOI: 10.1186/1756-3305-5-53 (cit. on p. 10).

Taticheff S, Kebede A, Bulto T, Werkeneh W, and Tilahun D (1994). Effect of ivermectin (Mectizan) on intestinal nematodes. *Ethiop Med J* 32.1, 7–15 (cit. on pp. 95, 101).

Taylor HR, Katala S, Muñoz B, and Turner V (1991). Increase in mortality associated with blindness in rural Africa. *Bull World Health Organ* 69.3, 335–338 (cit. on p. 10).

Taylor HR, Munoz B, Keyvan-Larijani E, and Greene BM (1989). Reliability of detection of microfilariae in skin snips in the diagnosis of onchocerciasis. *Am J Trop Med Hyg* 41.4, 467–471 (cit. on p. 7).

Taylor HR, Jonas JB, Keeffe J, Leasher J, Naidoo K, Pesudovs K, and Resnikoff S (2013). Disability weights for vision disorders in Global Burden of Disease study. *Lancet* 381.9860, 23. DOI: 10.1016/S0140-6736(12)62081-9 (cit. on p. 90).

Taylor MJ, Hoerauf A, and Bockarie M (2010). Lymphatic filariasis and onchocerciasis. *Lancet* 376.9747, 1175–1185. DOI: 10.1016/S0140-6736(10)60586-7 (cit. on p. 102).

Tchakouté VL, Graham SP, Jensen SA, Makepeace BL, Nfon CK, Njongmeta LM, Lustigman S, Enyong PA, Tanya VN, Bianco AE, and Trees AJ (2006). In a bovine model of onchocerciasis, protective immunity exists naturally, is absent in drug-cured hosts, and is induced by vaccination. *Proc Natl Acad Sci U S A* 103.15, 5971–5976. DOI: 10.1073/pnas.0601385103 (cit. on p. 145).

Tekle AH, Elhassan E, Isiyaku S, Amazigo UV, Bush S, Noma M, Cousens S, Abiose A, and Remme JH (2012). Impact of long-term treatment of onchocerciasis with ivermectin in Kaduna State, Nigeria: first evidence of the potential for elimination in the operational area of the African Programme for Onchocerciasis Control. *Parasit Vectors* 5, 28. DOI: 10.1186/1756-3305-5-28 (cit. on pp. 23, 81, 113, 114, 130).

Tekle AH, Zoure H, Wanji S, Leak S, Noma M, Remme JHF, and Amazigo U (2011). Integrated rapid mapping of onchocerciasis and loiasis in the Democratic Republic of Congo: impact on control strategies. *Acta Trop* 120 Suppl 1, S81–S90. DOI: 10.1016/j.actatropica.2010.05.008 (cit. on p. 148).

Thylefors B (2008). The Mectizan Donation Program (MDP). *Ann Trop Med Parasitol* 102 Suppl 1, 39–44. DOI: 10.1179/136485908X337481 (cit. on p. 10).

Thylefors B and Tønjum AM (1980). A three-year follow-up of ocular onchocerciasis in an area of vector control. *Bull World Health Organ* 58.1, 107–112 (cit. on p. 3).

Tielsch JM and Beeche A (2004). Impact of ivermectin on illness and disability associated with onchocerciasis. *Trop Med Int Health* 9.4, A45–A56. DOI: 10.1111/j.1365-3156.2004.01213.x (cit. on pp. 16, 76, 95).

Traore MO, Sarr MD, Badji A, Bissan Y, Diawara L, Doumbia K, Goita SF, Konate L, Mounkoro K, Seck AF, Toe L, Toure S, and Remme JHF (2012). Proof-of-principle of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: final results of a study in Mali and Senegal. *PLoS Negl Trop*

Dis 6.9, e1825. DOI: 10.1371/journal.pntd.0001825 (cit. on pp. 23, 79, 81, 82).

Traoré-Lamizana M and Lemasson J.-J (1987). Participation to a feasability study for the onchocerciasis control in the Logone Basin area. *Simulium damnosum* complex species distribution in the Cameroonian area of the project. [Participation à une étude de faisabilité d'une campagne de lutte contre l'onchocercose dans la région de bassin de Logone. Répartition des espèces du complexe *Simulium damnosum* dans la zone camerounaise du projet.] *Cah ORSTOM* 25, 171–186 (cit. on pp. 25, 26).

Traoré-Lamizana M, Somiari S, Mafuyai HB, Vajime CG, and Post RJ (2001). Sex chromosome variation and cytotaxonomy of the onchocerciasis vector Simulium squamosum in Cameroon and Nigeria. *Med Vet Entomol* 15.2, 219–223 (cit. on pp. 25, 27).

Umeh RE, Mahmoud AO, Hagan M, Wilson M, Okoye OI, Asana U, Biritwum R, Ogbu-Pearce P, Elhassan E, Yaméogo L, Braideo EI, and Seketeli A (2010). Prevalence and distribution of ocular onchocerciasis in three ecological zones in Nigeria. *Afr J Med Med Sci* 39.4, 267–275 (cit. on p. 47).

Usha V and Gopalakrishnan Nair TV (2000). A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. *J Am Acad Dermatol* 42.2 Pt 1, 236–240. DOI: 10.1016/S0190-9622(00)90131-2 (cit. on p. 102).

Vajime CG and Gregory WG (1990). Species complex of vectors and epidemiology. *Acta Leiden* 59.1-2, 235–252 (cit. on pp. 25, 27).

van Baal PHM, Hoeymans N, Hoogenveen RT, de Wit GA, and Westert GP (2006). Disability weights for comorbidity and their influence on health-adjusted life expectancy. *Popul Health Metr* 4, 1. DOI: 10.1186/1478-7954-4-1 (cit. on pp. 50, 59).

Van der Lelij A, Rothova A, Klaassen-Broekema N, Wilson WR, Barbe RF, and Stilma JS (1990). Decrease in adverse reactions after repeated ivermectin treatment in onchocerciasis. *Doc Ophthalmol* 75.3-4, 215–224 (cit. on p. 9).

van der Werf MJ, de Vlas SJ, Brooker S, Looman CWN, Nagelkerke NJD, Habbema JDF, and Engels D (2003). Quantification of

clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Trop* 86.2-3, 125–139 (cit. on p. 59).

Vivas-Martínez S, Basáñez MG, Botto C, Villegas L, García M, and Curtis CF (2000). Parasitological indicators of onchocerciasis relevant to ivermectin control programmes in the Amazonian focus of Southern Venezuela. *Parasitology* 121 Pt 5, 527–534 (cit. on pp. 24, 30).

Walker M, Little MP, Wagner KS, Soumbey-Alley EW, Boatin BA, and Basáñez M.-G (2012). Density-dependent mortality of the human host in onchocerciasis: relationships between microfilarial load and excess mortality. *PLoS Negl Trop Dis* 6.3, e1578. DOI: 10.1371/journal.pntd.0001578 (cit. on pp. 10, 76, 145).

Walsh J (1987). Merck donates drug for river blindness. *Science* 238.4827, 610 (cit. on p. 10).

Wanji S, Tendongfor N, Nji T, Esum M, Che JN, Nkwescheu A, Alassa F, Kamnang G, Enyong PA, Taylor MJ, Hoerauf A, and Taylor DW (2009). Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of co-endemicity with loiasis in Cameroon. *Parasit Vectors* 2.1, 39. DOI: 10.1186/1756-3305-2-39 (cit. on pp. 10, 148).

Wen L.-Y, Yan X.-L, Sun F.-H, Fang Y.-Y, Yang M.-J, and Lou L.-J (2008). A randomized, double-blind, multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China. *Acta Trop* 106.3, 190–194. DOI: 10.1016/j.actatropica.2008.03.007 (cit. on pp. 100, 101).

Whitworth JA and Gemade E (1999). Independent evaluation of onchocerciasis rapid assessment methods in Benue State, Nigeria. *Trop Med Int Health* 4.1, 26–30 (cit. on p. 24).

Whitworth JA, Gilbert CE, Mabey DM, Maude GH, Morgan D, and Taylor DW (1991a). Effects of repeated doses of ivermectin on ocular onchocerciasis: community-based trial in Sierra Leone. *Lancet* 338.8775, 1100–1103 (cit. on p. 176).

Whitworth JA, Gilbert CE, Mabey DM, Morgan D, and Foster A (1993). Visual loss in an onchocerciasis endemic community in Sierra Leone. *Br J Ophthalmol* 77.1, 30–32 (cit. on p. 176).

Whitworth JA, Morgan D, Maude GH, McNicholas AM, and Taylor DW (1991b). A field study of the effect of ivermectin on intestinal

helminths in man. *Trans R Soc Trop Med Hyg* 85.2, 232–234 (cit. on pp. 100, 101).

WHO (1980). *Methods of assessment of avoidable blindness.* Tech. rep. WHO Offset Publication No 54. World Health Organization (cit. on pp. 4, 46, 60).

WHO (1987). WHO Expert Committee on Onchocerciasis. Third report. *World Health Organ Tech Rep Ser* 752, 1–167 (cit. on pp. 4, 11).

WHO (1992). *Methods for the community diagnosis of onchocerciasis to guide ivermectin-based control in Africa.* TDR/TDR/ONCHO/92.2. World Health Organization (cit. on pp. 25, 26).

WHO (1995). Onchocerciasis and its control. Report of a WHO Expert Committee on Onchocerciasis Control. *World Health Organ Tech Rep Ser* 852, 1–104 (cit. on p. 59).

WHO (2004). Global Burden of Disease update 2004: disability weights for diseases and conditions. World Health Organization (cit. on pp. 49, 69, 87, 88, 183).

WHO (2006). *Preventive chemotherapy in human helminthiasis. Coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers.* ISBN: 92 4 154710 3 (cit. on pp. 109, 150).

WHO Commission on Macroeconomics and Health (2001). *Macroeconomics and health: investing in health for economic development. Report of the Commision on Macroeconomics and Health.* World Health Organization (cit. on p. 80).

Williams SCP (2012). Nodding syndrome leaves baffled scientists shaking their heads. *Nat Med* 18.3, 334. DOI: 10.1038/nm0312-334 (cit. on p. 6).

Winkler AS, Friedrich K, König R, Meindl M, Helbok R, Unterberger I, Gotwald T, Dharsee J, Velicheti S, Kidunda A, Jilek-Aall L, Matuja W, and Schmutzhard E (2008). The head nodding syndrome–clinical classification and possible causes. *Epilepsia* 49.12, 2008–2015. DOI: 10.1111/j.1528-1167.2008.01671.x (cit. on p. 6).

Winnen M, Plaisier AP, Alley ES, Nagelkerke NJD, van Oortmarssen G, Boatin BA, and Habbema JDF (2002). Can ivermectin mass treatments eliminate onchocerciasis in Africa? *Bull*

World Health Organ 80.5, 384–391 (cit. on pp. 16, 18, 19, 23, 82, 113, 114, 116, 131, 146).

Woolhouse ME (1998). Patterns in parasite epidemiology: the peak shift. *Parasitol Today* 14.10, 428–434 (cit. on p. 145).

Workneh W, Fletcher M, and Olwit G (1993). Onchocerciasis in field workers at Baya Farm, Teppi Coffee Plantation Project, southwestern Ethiopia: prevalence and impact on productivity. *Acta Trop* 54.2, 89–97 (cit. on pp. 11, 82).

Xia ZH, Su YL, Yao SY, Shen BR, Wen LY, Song CC, Wu ZK, Zou YC, Meng JC, and Yang HL (1992). [Clinical observation on efficacy of ivermectin in the treatment of intestinal nematode infections]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi* 10.4, 279–282 (cit. on p. 101).

Yaméogo L (2008). Special intervention zones. *Ann Trop Med Parasitol* 102 Suppl 1, 23–24. DOI: 10.1179/136485908X337445 (cit. on p. 13).

Yee TW and Wild CJ (1996). Vector Generalized Additive Models. *Journal of Royal Statistical Society, Series B* 58.3, 481–493 (cit. on p. 168).

Yelifari L, Bloch P, Magnussen P, van Lieshout L, Dery G, Anemana S, Agongo E, and Polderman AM (2005). Distribution of human Oesophagostomum bifurcum, hookworm and Strongyloides stercoralis infections in northern Ghana. *Trans R Soc Trop Med Hyg* 99.1, 32–38. DOI: 10.1016/j.trstmh.2004.02.007 (cit. on p. 98).

Zimmerman PA, Dadzie KY, De Sole G, Remme J, Alley ES, and Unnasch TR (1992). *Onchocerca volvulus* DNA probe classification correlates with epidemiologic patterns of blindness. *J Infect Dis* 165.5, 964–968 (cit. on p. 28).

Zouré HGM, Wanji S, Noma M, Amazigo UV, Diggle PJ, Tekle AH, and Remme JHF (2011). The geographic distribution of *Loa loa* in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). *PLoS Negl Trop Dis* 5.6, e1210. DOI: 10.1371/journal.pntd.0001210 (cit. on pp. 108, 148).

Summary / Samenvatting

English summary

The research described in this thesis aims to quantify the health impact of onchocerciasis control in Africa. **Chapter 1** gives an introduction into onchocerciasis (river blindness), describing the life cycle of the worm causing the disease (*Onchocerca volvulus*), its symptoms, diagnosis, treatment, and past and ongoing control programs. Through vector control and ivermectin mass treatment, the Onchocerciasis Control Program (OCP, 1975–2002) has largely eliminated onchocerciasis from West Africa. In the remaining endemic parts of Africa (16 countries), onchocerciasis control is ongoing (since 1995) by means of annual ivermectin mass treatment, coordinated by the African Programme for Onchocerciasis Control (APOC). Because of limited resources, is it not feasible to monitor and evaluate the effect of control interventions everywhere. Therefore, to quantify the health impact of onchocerciasis control, we used a modeling approach linking available data on the pre-control distribution of infection to the known natural history of disease, data on the population coverage of mass treatment, and the known effects of mass treatment on infection and disease. This was done using the mathematical model ONCHOSIM, a microsimulation model that simulates a typical African village, its inhabitants, the transmission of worm infections between individuals, and the production of microfilariae (mf) and consequent morbidity within individuals. Furthermore, it simulates the impact of interventions such as vector control and mass treatment with ivermectin. In the past, ONCHOSIM has also been extensively used for program evaluation and decision support.

In the next two chapters, we investigate two topics in preparation of estimating the impact of onchocerciasis control. In **Chapter 2**, we describe a statistical analysis of the association between nodule prevalence in adult males and mf prevalence in the general population. Our quantification of this association allows data on pre-control nodule prevalence to be related to the large body of literature on the correlation between mf prevalence and prevalence of onchocercal morbidity, allowing better estimation of the disease burden of onchocerciasis. Furthermore, combined with information on coverage of mass treatment, this association allows data on nodule prevalence to be interpreted in terms of prospects of elimination.

In **Chapter 3**, we describe patterns in concurrence of eye and skin symptoms due to onchocerciasis in persons. This information is important for correct estimation of the disease burden of onchocerciasis, as the burden of any given symptom may be influenced by the presence of a second symptom. We found significant concurrence of skin depigmentation and visual impairment, and of reactive skin disease and troublesome itch. Our results suggest a possible role of host characteristics in the pathogenesis of depigmentation and visual impairment. Further, we propose a method to deal with concurrence when estimating the burden of disease.

In the three subsequent chapters, we report the health impact of APOC. **Chapter 4** and **Chapter 5** present the estimated health impact of onchocerciasis control in APOC areas, based on a simulation study using ONCHOSIM. Based on data on pre-control infection levels and the history of mass treatment in APOC areas, we simulated the impact of ivermectin mass treatment on the burden of onchocerciasis due to visual impairment, blindness, and troublesome itch. We estimated that ivermectin mass treatment has reduced the disease burden due to onchocericasis in APOC target areas from 23.1 disability-adjusted life years (DALYs) per 1,000 persons (1995) to 8.6 DALYs per 1,000 persons (2010), and will further reduce the disease burden to 3.7 DALYs per 1,000 persons by 2015. Cumulatively, ivermectin mass treatment was estimated to have averted 8.9 million DALYs between 1995 and 2010, and to further avert 10.1 million DALYs between 2011 and 2015 in APOC target areas. This health impact was estimated to come at a cost of about US$30 per DALY averted, which is comparable to the cost of other large scale control programs against tropical infectious diseases, and indicates high cost-effectiveness of ivermectin mass treatment. In **Chapter 6** we present the estimated impact of APOC activities on off-target diseases, such as soil-transmitted helminths and ectoparasitic infections. We estimated the APOC has cumulatively averted about 500 thousand DALYs due to off-target diseases between 1995 and 2010.

In **Chapter 7**, we present the estimated impact of increasing mass treatment frequency on the prospects of elimination of onchocerciasis, and the associated program duration and number of mass treatment rounds. This information is timely as APOC has re-

cently changed its objective from morbidity control to elimination of infection, where possible, and is considering to increase the frequency of ivermectin mass treatment. We predict that increasing mass treatment frequency will shorten program duration required to achieve elimination by 40 % (6-monthly treatment) or 60 % (3-monthly treatment). This reduction always comes at a cost of additional treatment rounds required to achieve elimination. We recommend that high frequency mass treatment is only considered in areas where annual treatment is expected to take a long time to achieve elimination in spite of good treatment coverage, e.g. because of unfavorable transmission conditions or because mass treatment started recently. In low coverage settings, the first priority should be to increase the treatment coverage rather than increasing frequency. The benefits of increasing mass treatment frequency will be highly dependent on maintained coverage, and could be completely nullified if coverage of mass treatment were to fall in the future.

Finally, in **Chapter 8**, we summarize our findings, discuss the methodological aspects, and identify future research needs, leading to the following conclusions and recommendations:

Conclusions

1. Onchocerciasis control has had a considerable impact on population health in Africa, preventing disability due to eye and skin disease, and premature mortality associated with blindness.

2. Mass treatment with ivermectin is a highly cost-effective public health intervention against onchocerciasis.

3. Onchocercal skin disease and the associated itch are important contributors to the disease burden of onchocerciasis, but are not yet fully captured in existing estimates of the burden of onchocerciasis.

4. In low coverage settings, increasing mass treatment coverage is just as effective for achieving elimination as increasing mass treatment frequency, though costs fewer mass treatment rounds.

5. The health impact of APOC has been made possible through contributions by many different (inter)national and local stakeholders and funding parties, and close collaboration between policy makers and scientists.

6. Central registration of data on pre-control infection levels and the history of ivermectin mass treatment have provided pivotal input for the quantification of the health impact of APOC.

Recommendations for policy

1. Elimination of African onchocerciasis can only be achieved with intensified support from all stakeholders and funding parties, and through continued close collaboration between scientists and policy makers.

2. Increasing mass treatment frequency should only be considered in areas where annual treatment is not expected to achieve elimination by 2025 despite good coverage.

3. National control programs should maintain high program coverage and ensure accuracy of data on population coverage of mass treatment and human migration.

Recommendations for scientific research

1. In light of elimination of African onchocerciasis, there is a need for more information on migration of humans and *Simulium* flies in Central Africa.

2. To accurately predict program duration required for elimination of onchocerciasis, there is a need to quantify systematic non-compliance to mass treatment and inter-individual variation in exposure to infection.

3. It should be clarified whether local transmission is taking place in hypoendemic areas, and if so, how this is possible.

4. More sensitive tests for presence of *O. volvulus* infection are needed to monitor progress towards elimination and verify interruption of transmission.

5. Further development of alternative drugs such as doxycyclin and flubendazole can help to deal with loiasis co-endemicity and possible emergence of worm resistance against ivermectin.

6. ONCHOSIM should be further developed, incorporating information on disfiguring skin disease, transmission dynamics in settings of low intensity infection, migration of human and flies, and new diagnostic techniques and intervention strategies.

Nederlandse samenvatting

Het in dit proefschrift beschreven onderzoek heeft als doel om vast te stellen hoe groot de gezondheidseffecten van onchocerciasis bestrijding in Afrika zijn. **Hoofdstuk 1** geeft een introductie tot onchocerciasis (rivierblindheid) en beschrijft de levenscyclus van de worm die de ziekte veroorzaakt (*Onchocerca volvulus*), de symptomen, diagnose, behandeling, en lopende of reeds afgerond bestrijdingsprogramma's. Door middel van het bestrijden van vliegen die de infectie overdragen (vector bestrijding) heeft het Onchocerciasis Control Program (OCP, 1975–2002) onchocerciasis reeds geëlimineerd in het overgrote deel van West Afrika. In de gebieden in Afrika waar de infectie nog voorkomt (16 landen), wordt onchocerciasis sinds 1995 bestreden door middel van jaarlijks massabehandelingen met het medicijn ivermectine, wat gecoördineerd wordt door het African Programme for Onchocerciasis Control (APOC). Vanwege de beperkte hoeveelheid middelen in Afrika is het niet mogelijk om de effecten van onchocerciasis bestrijding overal te monitoren. Om de gezondheidseffecten van onchocerciasis bestrijding te kwantificeren, hebben we daarom een model gebruikt waarmee we beschikbare data over de geografische spreiding van infectie (voor aanvang van bestrijdingsmaatregelen) hebben gekoppeld aan data over de geschiedenis van bestrijdingsmaatregelen, en kennis over de transmissie en het natuurlijk verloop van de ziekte en de effecten van bestrijdingsmaatregelen hierop. Dit is gedaan in het wiskundig model ONCHOSIM, een microsimulatie model dat een typisch Afrikaans dorp simuleert, inclusief de individuele bewoners van het dorp, de overdracht van worminfecties tussen personen, de productie van microfilariae (worm-

larven), en symptomen die resulteren als gevolg van blootstelling aan infectie. Daarnaast simuleert ONCHOSIM de effecten van vector bestrijding en massabehandeling met ivermectine in het dorp. In het verleden is ONCHOSIM herhaaldelijk gebruikt voor het evalueren van bestrijdingsmaatregelen en het maken dan wel aanpassen van bestrijdingsbeleid.

In de volgende twee hoofdstukken worden twee onderwerpen behandeld als voorbereiding op het schatten van de gezondheidseffecten van onchocerciasis bestrijding. In **Hoofdstuk 2** wordt een statistische analyse beschreven die betrekking heeft op de associatie tussen de proportie volwassen mannen in een dorp met onderhuidse knobbels (als gevolg van infectie) en de proportie van de algemene bevolking in een dorp met detecteerbare microfilariae in de huid. De resultaten van deze analyse kunnen worden gebruikt om data over de geografische spreiding van infectie (voor aanvang van bestrijdingsmaatregelen) te interpreteren in termen van kans op eliminatie, wanneer gecombineerd met informatie over bestrijdingsmaatregelen.

In **Hoofdstuk 3** wordt beschreven volgens welke patronen oogen huidziekte (door onchocerciasis) tegelijk voorkomen in personen. Deze patronen zijn belangrijk voor het correct schatten van de ziektelast van onchocerciasis, omdat de ziektelast van één symptoom beïnvloed kan worden door de aanwezigheid van een tweede symptoom. We concluderen dat depigmentatie (huidontkleuring) en gezichtverlies relatief vaak in dezelfde personen voorkomen, en dat reactieve huidziekte en jeuk vaak samen voorkomen. Verder spelen eigenschappen van de menselijke gastheer mogelijk een rol in het wel of niet ontwikkelen van zowel depigmentatie als gezichtsverlies. Ten slotte stellen we een methode voor waarmee bij het schatten van de ziektelast van onchocerciasis rekening gehouden kan worden met het tegelijk voorkomen van symptomen.

In de drie volgende hoofdstukken rapporteren we de gezondheidseffecten van massabehandeling met ivermectine, georganiseerd door APOC. **Hoofdstuk 4** en **Hoofdstuk 5** beschrijven de gezondheidswinst ten gevolge van APOC, gebaseerd op een simulatie studie met ONCHOSIM. Hiervoor hebben we de gevolgen van massabehandeling met ivermectine op slechtziendheid, blindheid, en jeuk gesimuleerd, gebaseerd op data over de geografische spreiding van in-

fectie en de geschiedenis van bestrijdingsmaatregelen. Volgens onze schattingen heeft massabehandeling met ivermectine de ziektelast van onchocerciasis in APOC gebieden verlaagd van ongeveer 23.1 gezonde levensjaren verloren per 1,000 mensen in 1995 naar 8.6 gezonde levensjaren verloren per 1,000 mensen in 2010. In 2015 zal de ziektelast naar verwachting verder gedaald zijn tot 3.7 gezonde levensjaren verloren per 1,000 mensen. Bij elkaar opgeteld heeft APOC tussen 1995 en 2010 8.9 miljoen gezonde levensjaren gered, en zal naar verwachting nog eens 10.1 gezonde levensjaren redden tussen 2011 en 2015. Deze gezondheidseffecten hebben ongeveer US$30 per gewonnen gezond levensjaar gekost, wat betekent dat massabehandeling met ivermectine een zeer kosten-effectieve bestrijdingsmaatregel is. Verder zijn de kosten per gewonnen levensjaar vergelijkbaar met die van bestrijdingsprogramma's tegen andere tropische infectieziekten. In **Hoofdstuk 6** schatten we de gezondheidseffecten van APOC gerelateerd aan de effecten van massabehandeling met ivermectine op andere infectieziekten dan onchocerciasis, zoals bijvoorbeeld intestinale worminfecties en schurft. Bij elkaar heeft APOC tussen 1995 en 2010 ongeveer 500 duizend gezonde levensjaren gered die anders verloren waren als gevolg van andere infecties dan onchocerciasis.

In **Hoofdstuk 7** wordt besproken hoe het verhogen van de frequentie van massabehandelingen met ivermectine de duur van eliminatieprogramma's tegen onchocerciasis zou kunnen verkorten, en onder welke omstandigheden. Deze informatie is zeer belangrijk gegeven dat APOC recent zijn doel heeft bijgesteld van het voorkomen van ziekte naar het elimineren van infectie zodat bestrijdingsmaatregelen kunnen stoppen, en overweegt om in sommige regio's de frequentie van massabehandelingen te verhogen. Wij voorspellen dat het verdubbelen van de frequentie van massabehandelingen zal leiden tot een reductie in programmaduur van ongeveer 40 %, en dat een verviervoudiging van de frequentie zal leiden tot een reductie van duur van ongeveer 60 %. Daar staat tegenover dat het verhogen van de frequentie van massabehandeling uiteindelijk altijd zal leiden tot een hoger aantal benodigde massabehandelingsronden om eliminatie bereiken. Wij adviseren dat het verhogen van de frequentie alleen overwogen moet worden in gebieden waarvan verwacht wordt dat eliminatie nog lang niet bereikt is ondanks een hoge dekkingsgraad van

massabehandeling, bijvoorbeeld omdat de overdracht van infectie in een gebied relatief hoog ligt (door aanwezigheid van veel *Simulium* vliegen) of omdat massabehandelingen slechts recent zijn begonnen. In gebieden waar de dekkingsgraad van massabehandeling nog laag is, moet deze eerst verhoogd worden voordat overwogen wordt de frequentie te verhogen. De positieve effecten van hoog-frequente massabehandeling zijn sterk afhankelijk van het behouden van een goede dekkingsgraad, en zouden compleet tenietgedaan kunnen worden als de dekkingsgraad daalt.

Tot slot worden in **Hoofdstuk 8** alle bevindingen samengevat, methodologische aspecten besproken, en belangrijke onderwerpen voor verder onderzoek genoemd, leidend tot de volgende conclusies en aanbevelingen:

Conclusies

1. Onchocerciasis bestrijding heeft middels het voorkómen van oog- en huidziekte en oversterfte onder blinde mensen een aanzienlijk effect gehad op de volksgezondheid in Afrika.

2. Massabehandeling met ivermectin is een zeer kosten-efficiënte bestrijdingsmaatregel tegen onchocerciasis.

3. Huidziekte en bijkomende jeuk dragen het meeste bij aan de ziektelast van onchocerciasis, en zijn nog niet geheel vertegenwoordigd in huidige schattingen van de ziektelast van onchocerciasis.

4. In gebieden waar de dekkingsgraad van massabehandeling met ivermectin laag is, is het verhogen van de dekkingsgraad net zo efficient in het bereiken van eliminatie als het verhogen van de frequentie van massabehandeling, doch kost uiteindelijk minder massabehandelingsronden.

5. De gezondheidseffecten als gevolg van APOC zijn mogelijk gemaakt door de betrokkenheid van veel verschillende (inter)nationale en lokale partijen en donoren, en goede samenwerking tussen beleidsmakers en wetenschappers.

6. Het centraal registeren van de geografische spreiding van infectie voor aanvang van bestrijdingsmaatregelen en de geschiedenis van massabehandeling zijn cruciaal geweest voor het kwantificeren van de gezondheidseffecten van APOC.

Aanbevelingen voor beleid

1. Eliminatie van onchocerciasis in Afrika is alleen mogelijk met verhoogde support van alle betrokken partijen en donoren, en met blijvende samenwerking tussen wetenschappers en beleidsmakers.

2. Het verhogen van de frequentie van massabehandeling met ivermectine moet alleen overwogen worden in gebieden waar jaarlijkse behandeling niet tot eliminatie zal leiden voor 2025, ondanks een hoge dekkingsgraad.

3. Nationale bestrijdingsprogramma's moeten een adequate dekkingsgraad van massabehandeling waarborgen en nauwkeurig data bijhouden over de dekkingsgraad en migratie van mensen.

Aanbevelingen voor wetenschappelijk onderzoek

1. Om onchocerciasis te kunnen elimineren in Afrika, moet de migratie van mensen en *Simulium* vliegen in Afrika beter in kaart gebracht worden.

2. Om precieze voorspellingen te kunnen doen over wanneer onchocerciasis geëlimineerd zal zijn, moet eerst vastgesteld worden hoe groot systematische non-participatie van mensen in massabehandelingen is en hoe hoog de variatie tussen mensen in blootstelling aan vliegenbeten is.

3. Er moet uitgezocht worden of lokale transmissie van infectie plaatsvindt in hypoendemische gebieden, en zo ja, hoe dit mogelijk is.

4. Om de progressie van eliminatie van onchocerciasis te monitoren zijn er gevoeligere testen nodig om infectie met *O. volvulus* te kunnen vaststellen.

5. De ontwikkeling van alternatieve medicijnen tegen onchocerciasis zoals doxycycline en flubendazol kan helpen om onchocerciasis te bestrijden in gebieden waar loiasis voorkomt, en gebieden waar wormen in de toekomst mogelijk resistent tegen ivermectine worden.

6. ONCHOSIM moet uitgebreid worden, waarbij een breder spectrum aan huidziektes, mogelijk alternatieve transmissie mechanismen in hypoendemische gebieden, migratie van mensen en vliegen, en nieuwe diagnostische technieken en bestrijdingsmaatregelen geïncorporeerd moeten worden in het model.

Dankwoord / Acknowledgements

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Roel, bedankt voor je support bij het updaten en debuggen van WORMSIM. Onze overleggen werden steevast voorafgegaan door discussies over leuke technische vraagstukken. Wie weet slepen we nog een keer zo'n Kaggle prijs binnen.

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About the author

Curriculum vitae

Luc Coffeng was born on July 6^{th}, 1982 in Utrecht, The Netherlands. In 2000, Luc passed his secondary school exams at the Herman Jordan Montessori Lyceum in Zeist, and started studying Artificial Intelligence at the Free University in Amsterdam. A year later, having reconsidered his choice of study, Luc started studying Medicine at Utrecht University, and obtained his M.D. in 2007. During his studies, he fostered an interest in research while working on research projects in psychoneuroendocrinology, HIV genetics, and medical education. As a medical student, Luc also started volunteering for the foundation Medical Checks for Children, where he remains active to this day, working on the coordination and evaluation of health camps for deprived children in Ladakh, India. From 2008 to 2013, Luc worked as a PhD student in Epidemiology and Mathematical Biology at the Department of Public Health at Erasmus MC, Rotterdam. In 2009, Luc was voted PhD student of the year of the Erasmus University. In 2011, he obtained his Master of Science in Epidemiology at the Netherlands Institute of Health Sciences in Rotterdam. During his PhD period, he has cumulatively spent three months at the Department of Infectious Disease Epidemiology at Imperial College London, and has made frequent working visits to the headquarters of the African Programme for Onchocerciasis Control in Ouagadougou, Burkina Faso. Furthermore, he has been an invited speaker at several expert meetings on the elimination of African onchocerciasis. In September 2013, Luc started working as a Senior Research Fellow at the Institute for Health Metrics and Evaluation at the University of Washington in Seattle, United States of America.

List of publications

This thesis

Coffeng LE, Fobi G, Ozoh G, Bisseck A, Nlatte B, Enyong P, Olinga JMO, Zoure HGM, Habbema JDF, Stolk WA, de Vlas SJ, Boussinesq M, Noma M (2012). Concurrence of dermatological and ophthalmological morbidity in onchocerciasis. *TRSTMH* 160:243–251. doi: 10.1016/j.trstmh.2011.12.006

Coffeng LE, Pion SDS, O'Hanlon S, Cousens S, Abiose AO, Fischer P, Remme JHF, Dadzie KY, Murdoch ME, de Vlas SJ, Basáñez M-G, Stolk WA, Boussinesq M (2013). Onchocerciasis: the pre-control association between prevalence of palpable nodules and skin microfilariae. *PLoS Negl Trop Dis* 7:e2168. doi: 10.1371/journal.pntd.0002168

Coffeng LE, Stolk WA, Zouré HGM, Veerman JL, Agblewonu KB, Murdoch ME, Noma M, Fobi G, Richardus JH, Bundy DAP, Habbema JDF, de Vlas SJ, Amazigo UV (2013). African Programme for Onchocerciasis Control 1995-2015: model-estimated health impact and cost. *PLoS Negl Trop Dis* 7:e2032. doi: 10.1371/journal.pntd.0002032

Coffeng LE, Stolk WA, Zouré HGM, Veerman JL, Agblewonu KB, Murdoch ME, Noma M, Fobi G, Richardus JH, Bundy DAP, Habbema JDF, de Vlas SJ, Amazigo UV (submitted). African Programme for Onchocerciasis Control 1995–2015: updated estimates of the health impact based on new disability weights.

Krotneva S, Coffeng LE, Noma M, Zouré HGM, Bakoné M, Amazigo UV, de Vlas SJ, Stolk WA (submitted). African Programme for Onchocerciasis Control: impact of annual ivermectin mass treatment on off-target infectious diseases.

Coffeng LE, de Vlas SJ, Hopkins AD, Stolk WA (submitted). Elimination of African onchocerciasis: modeling the impact of increasing the frequency of ivermectin mass treatment.

Other publications

Ter Wolbeek M, van Doornen LJ, Coffeng LE, Kavelaars A, Heijnen CJ (2007). Cortisol and severe fatigue: a longitudinal study in adolescent girls. *Psychoneuroendocrinology* 32:171–182. doi:

10.1016/j.psyneuen.2006.12.003

Coffeng LE, Visscher AJE, ten Cate ThJ (2009). Early clinical experiences affect career preference in male but not in female students. *Medical Teacher* 31: e323–e326. doi: 10.1080/01421590802650084

Murray CJL, Vos Th, Lozano R, ..., Coffeng LE, ..., et al (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380:2197–2223. doi: 10.1016/S0140-6736(12)61689-4

Lozano R, Naghavi M, Foreman K, ..., Coffeng LE, ..., et al (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0

Vos Th, Naghavi M, Lozano R, ..., Coffeng LE, ..., et al (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380:2163–2196. doi: 10.1016/S0140-6736(12)61729-2

Vendrig JC, Coffeng LE, Fink-Gremmels J (2012). Equine colostral carbohydrates reduce the lipopolysaccharide-induced inflammatory response in equine peripheral blood mononuclear cells. *Equine Vet J* 44 Suppl 43:68-72. doi: 10.1111/j.2042-3306.2012.00680.x

Vendrig JC, Coffeng LE, Fink-Gremmels J (2013). Effects of separate and concomitant TLR-2 and TLR-4 activation in peripheral blood mononuclear cells of newborn and adult horses. *PLoS One* 8:e66897.

Vendrig JC, Coffeng LE, Fink-Gremmels J (2013). In vitro evaluation of defined oligosaccharide fractions in an equine model of inflammation. *BMC Vet Res* 9:147. [Epub ahead of print]

PhD portfolio

Name PhD-student:	Luc E. Coffeng
Erasmus MC department:	Department of Public Health
PhD-period:	2008–2013
Supervisor:	Prof.dr. J.H. Richardus
Advisors:	Dr. W.A. Stolk
	Dr. S.J. de Vlas

	Period	Workload
Master of Health Sciences (specialization in Epidemiology), Netherlands Institute for Health Sciences		
Erasmus Summer Program		
Principles of Research in Medicine	2008	20 hrs.
Methods of Public Health Research	2008	20 hrs.
Health Economics	2008	20 hrs.
Conceptual Foundation of Epidemiologic Study Design	2008	20 hrs.
Case-control Studies	2008	20 hrs.
Introduction to Public Health	2008	20 hrs.
Methods of Health Services Research	2009	20 hrs.
Principles of Genetic Epidemiology	2009	20 hrs.
Primary and Secondary Prevention Research	2009	20 hrs.
Introduction to Decision-making in Medicine	2009	20 hrs.
Demography of Ageing	2009	20 hrs.
History of Epidemiologic Ideas	2010	20 hrs.
Core Curriculum		
Study Design	2008	120 hrs.
Classical Methods for Data analysis	2009	160 hrs.
Methodologic Topics in Epidemiologic Research	2009	40 hrs.
Modern Statistical Methods	2009	120 hrs.
Public Health Research Methods	2008	160 hrs.
Advanced short courses		
Epidemiology of Infectious Diseases	2009	40 hrs.
Bayesian Statistics	2010	30 hrs.
Advanced Topics in Decision-making in Medicine	2011	53 hrs.
Repeated Measurements in Clinical Studies	2009	53 hrs.

	Period	Workload
Awards		
Erasmus University Rotterdam PhD-Student of the Year	2009	
Conference presentations		
Oral presentation "Correlation of dermatological and ophthalmological morbidity in onchocerciasis (forest type)". NVTG Symposium, Utrecht, The Netherlands	2009	24 hrs.
Oral presentation nominated for Young Investigator Award "Correlation of dermatological and ophthalmological morbidity in onchocerciasis (forest type)". 58^{th}Annual meeting of the American Society of Tropical Medicine and Hygiene, Washington, DC, USA	2009	24 hrs.
Oral presentation "The Global Burden of Disease Project: pre-control burden of onchocercal eye disease in APOC areas". NVTG Symposium, Utrecht, The Netherlands	2010	24 hrs.
Poster presentation "Global Burden of Disease project: pre-control burden of onchocercal eye disease in African Programme for Onchocerciasis Control considerably higher than previously estimated". 59^{th} Annual meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, GA, USA	2010	24 hrs.
Oral presentation "African Programme for Onchocerciasis Control: impact and costs by 2010". 60^{th} Annual meeting of the American Society of Tropical Medicine and Hygiene, Philadelphia, PA, USA	2011	24 hrs.
Poster presentation: "From control to elimination of African onchocerciasis: should the frequency of ivermectin mass treatment be increased?" 61^{th} Annual meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, GA, USA	2012	24 hrs.
Expert meetings and workshops		
Invited participant in expert meeting on feasibility of elimination of onchocerciasis, Ouagadougou, Burkina Faso	2009	24 hrs.
Invited trainer in workshops on the use of ONCHOSIM for policy making in onchocerciasis control, Ouagadougou, Burkina Faso	2010-2011	180 hrs.
Invited speaker at the 47^{th} Meeting of the Mectizan Expert Committee, Geneva, Switzerland: 'Shifting the focus from onchocerciasis control to elimination: should the frequency of mass treatment be increased?'	2012	24 hrs.
Teaching activities		
Book club: *Mathematical Models in Biology* by Edelstein-Keshet	2009	40 hrs.
Examination of elective course Tropical Medicine & Public Health (essays)	2009–2012	360 hrs.
Committee member for Minor in Tropical Medicine & International Health	2009–2012	60 hrs.
Design and development of a serious game on Motivational Interviewing	2012–2013	60 hrs.
Lecture on vaccination techniques	2011-2012	60 hrs.
Introductory lecture on mathematical modeling: Onchocerciasis, can it be eliminated? What models tell us	2012	8 hrs.
Field work for Medical Checks for Children[a] **(volunteering)**		
Missions to Chitwan, Nepal	2008	80 hrs.
	2009	80 hrs.
Missions to Ladakh, India	2011	120 hrs.
	2012	120 hrs.
	2013	120 hrs.

[a] www.medicalchecksforchildren.org