Imperial College London

Projecting *Onchocerca volvulus* infection trends and times to onchocerciasis elimination using the EPIONCHO-IBM transmission model in Togo

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Completing this dissertation was an enlightening experience both on a professional and personal level.

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I am also sincerely grateful and pleased for the opportunity to collaborate with the Erasmus Medical Centre, Health & Development International Inc. (HDI), and the Togolese Ministry of Health by assisting Togo in reaching another milestone against neglected tropical diseases.

Lastly, I would like to acknowledge my family and friends for their understanding and encouragement.

Reflection Statement

I started the masters in epidemiology with a passion for microbes and a sense of their importance in public health. During the taught modules of the degree, I explored the diverse disciplines of epidemiology. The area that stimulated my interest was mathematical models applied to infectious diseases, particularly neglected tropical diseases. These diseases impact the lives of more than a billion people globally, especially in the poorest countries, trapping them in a cycle of poverty and illnesses. Hence, it was a great pleasure to implement my newly acquired knowledge to approach the Togolese Ministry of Health database in the fight against river blindness.

The last few months have been an enriching and unique experience. I expanded my understanding of mathematical modelling for vector-borne diseases, as well as its assumptions, advantages and limitations. I also learned to focus on the bigger picture and to attain the goals gradually. Before starting the thesis, I had an accelerated pace of work, which did not facilitate sharing the findings and knowledge. During meetings with my supervisors, I overpassed this challenge and developed further my presentation skills.

My expertise was developed in analyzing complex epidemiological situations involving a life cycle between two hosts and several stages (i.e. microfilariae, L3 larvae and adult worms) and

representing them in mathematical equations. One of the most significant tasks of this project was preparing the dataset to extract the inputs for the simulations. The data consolidation was a particularly long process. I had to harmonise the names and confirm the region of the villages, complement the SIZ status, remove duplicate surveys and define the duration of vector control and the start of ivermectin mass drug administration. An extensive literature review was needed to supplement some variables.

With this thesis, I hope to support Togo eliminate the transmission of river blindness. I aim to apply the skills I developed with this project to continue to assist the development of global health.

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List of Abbreviations

95% CI — 95% confidence interval

ABR — Annual biting rate

APOC — African Programme for Onchocerciasis Control

ATP — Annual transmission potential

ATS — Alternative treatment strategies

CDTI — Community-directed treatment with ivermectin

DALYs — Disability-adjusted life years

DRC — Democratic Republic of Congo

EoT — Elimination of transmission

EPHP — Elimination as a public health problem

MDA — Mass drug administration

MoH — Ministry of Health

NTDs — Neglected tropical diseases

OCP — Onchocerciasis Control Programme in West Africa

PES — Post-elimination surveillance

PNC — Probability of non-compliance

PTS — Post-treatment surveillance

REA — Rapid epidemiological assessment

REMO — Rapid epidemiological mapping of onchocerciasis

SAEs — Severe adverse events

SIZ — Special Intervention Zones

VC — Vector control

WHO — World Health Organization

Abstract

Onchocerciasis is a neglected tropical disease that burdens millions mostly in Africa, and is a substantial source of morbidity, disability and excess mortality. The parasite spreads between humans by the bites of blackfly vectors. Togo is endemic for onchocerciasis and has made considerable progress towards controlling the disease. The country was included in the OCP and the SIZ that followed OCP's closure in 2002. These programmes involved vector control (VC) and ivermectin MDA. Once OCP and SIZ ended, the Togolese Ministry of Health sustained the MDA programme. The control interventions were not equally implemented in the country, and only the three northern regions were partially incorporated in the SIZ.

Togo's MoH seeks to EoT of onchocerciasis by 2030. Hence, there is a need to investigate past and current epidemiological status and prospects of the country to achieve control/elimination, considering the history of interventions implemented and baseline endemicity levels. The central aim is to understand the temporal and spatial trends of *Onchocerca. volvulus* infection in Togo and identify foci that may have reached EoT or require ATS. Once EoT is deemed to have been achieved, stop-MDA surveys can be implemented.

The individual-based stochastic EPIONCHO-IBM transmission model, structured by host age and sex, was used to project infection trends for every region (Savanes, Kara, Centrale, Plateaux and Maritime) and SIZ status in Togo. Twelve scenarios were simulated for each setting, based on three scenarios of control interventions (optimistic, reference and pessimistic) and four baseline endemicity levels (30%, 50%, 70% and 90% microfilarial prevalence). The model was calibrated to determine ABR for each of the simulated baseline endemicities. Control interventions were simulated, with VC decreasing ABR during its duration, and with ivermectin exerting microfilaricidal, embryostatic and cumulative sterilizing effects on the parasite.

Model outputs highlighted the heterogeneous epidemiological situation in Togo. VC moderately impacted microfilarial prevalence, with the maximum reduction achieved in Savanes. Ivermectin MDA led to a marked decrease in prevalence. Initially hypoendemic and mesoendemic villages can proceed to implement stop-MDA surveys, while most hyperendemic and holoendemic communities may require additional years of intervention including ATS. SIZ villages from Kara and Centrale had the highest baseline prevalence and would require intensified control. Maritime can most likely proceed with stop-MDA surveys at the regional level, while Plateuax would need additional rounds

of MDA. Savanes may reach EoT by 2030 if ATS were promptly implemented. Kara and Centrale will likely require longer durations of interventions.

The EPIONCHO-IBM model has the advantage of being stochastic, valuable when villages are close to EoT, and of considering heterogeneity in exposure to blackfly bites. However, its inclusion of density-dependent processes governing the transmission of *O. volvulus* make it particularly resilient to control interventions. It assumes a moderate probability of systematic non-compliance, which decreases as MDA therapeutic coverage increases. As Togo approached EoT, surveillance will be essential to recognise resurgence, especially in previously hyperendemic zones. Ultimately, new diagnostic techniques, monitoring and evaluation of endemic villages, and high levels of MDA coverage and compliance will be essential to reach EoT.

1. Introduction, Literature Review and Aims of the Project

1.1 Onchocerciasis

Onchocerciasis, or river blindness, is an anthroponotic parasitic infection caused by the filarial nematode *Onchocerca volvulus* and transmitted among humans through bites of *Simulium* blackfly vectors (Burnham, 1998; Duke, 1990). The infection poses a substantial disease burden in endemic communities due to its ocular, cutaneous and neuro-hormonal sequelae, which are ultimately responsible for morbidity, disability, and excess mortality (Little *et al.*, 2004; Walker *et al.*, 2012; Pion, Kamgno & Boussinesq, 2002). The Global Burden of Disease Study estimated 1.23 (95% Uncertainty Interval 0.765–1.82) million disability-adjusted life years (DALYs) due to onchocerciasis in 2019 (Global Health Metrics, 2020). With no prophylactic vaccines or treatments (Hotez *et al.*, 2015), river blindness is the second infectious cause of blindness worldwide after trachoma (Koroma *et al.*, 2018) and one of the neglected tropical diseases (NTDs) targeted for elimination of transmission (EoT) by the World Health Organization (WHO) in its 2021–2030 roadmap on NTDs (Group, 2019; World Health Organization, 2020c). It is primarily prevalent in sub-Saharan Africa, where more than 99% of the estimated 21 million cases are found (Burki, 2021; World Health Organization, 2021).

1.2 *Onchocerca volvulus* Lifecycle

The dioecious adult worms of *O. volvulus* (macrofilariae) live in subcutaneous nodules (onchocercomas) in humans, which can contain several females and males (Roberts, Janovy & Schmidt, 2009; Burnham, 1998). Their average (reproductive) lifespan is about ten years (Plaisier *et al.*, 1991), although some worms are expected to live up to 20 years according to modelling projections (Milton *et al.*, 2020; Hamley *et al.*, 2019). Female fecundity is thought to be age-dependent, decreasing in older females (Karam *et al*., 1987; Plaisier *et al.*, 1991). On average, fertile and fertilised female worms produce one thousand microfilariae per day (Schulz-Key, 1990).

Microfilariae are the larval offspring of adult worms. With a lifespan of 12 to 18 months (Duke, 1968), they are responsible for the majority of the clinical manifestations associated with onchocerciasis (van Laethem & Lopes, 1996; Bradley, Whitworth & Basáñez, 2005) and are the stage infective to vectors. Microfilariae migrate to the subcutaneous tissue (skin lymphatics), ocular tissue (anterior and posterior segments of the eye), and in heavy infection intensity can also be found in

peripheral blood, urine and sputum (Anderson, Fazen & Buck, 1975). They are ingested by the *Simulium* vectors when they take a blood meal (Bradley, Whitworth & Basáñez, 2005). Those microfilariae that escape the peritrophic matrix formed around the blood meal migrate to the thoracic muscles of the fly. At this stage, they are denominated L1 larvae (Duke, 1990).

L1 ("sausage-stage") larvae moult into L2 ("pre-infective") larvae in the thorax of the fly; L2 larvae moult into L3 infective larvae (Hamley *et al.*, 2019), which migrate to the proboscis (mouthparts) of the insect and are inoculated into humans in a subsequent blood meal (Bradley, Whitworth & Basáñez, 2005). The transformation from microfilariae to L3 infective larvae takes up to two weeks (extrinsic incubation period), less than one week in tropical countries like Togo (Cheke *et al.*, 2015). Once the L3 larvae are inoculated into humans, they moult into L4 and L5 stages and mature into adult worms in 12 to 18 months (intrinsic incubation period) (Duke, 1993). The pre-patent period (until microfilariae are detectable in the skin) can take between 18 and 24 months (Prost, 1980).

1.3 Clinical Manifestations

In generalised onchocerciasis, most microfilariae evade the immune system when alive but induce an inflammatory response upon their death (van Laethem & Lopes, 1996). This response is driven by both parasite antigens and *Wolbachia* endosymbionts (Brattig, 2004). *Wolbachia pipientis* are endosymbiotic bacteria thought to be vital for the development, viability and reproduction of the worms (Tamarozzi *et al.*, 2011). *Wolbachia* are Gram-negative bacteria exhibiting lipopolysaccharide (LPS) endotoxins in their exterior cell wall, which activate the TLR4 immune pathway and strongly contribute to onchocerciasis eye disease (Bouchery *et al.*, 2013; saint André *et al.*, 2002; Hise, Gillette-Ferguson & Pearlman, 2003). Ocular manifestations range from conjunctivitis and photophobia to punctate ("snow-flake") and sclerosing keratitis ("corneal opacity") (Budden, 1962), with progressive visual loss leading to irreversible blindness (Hopking & Boatin, 2011). The posterior segment of the eye can also be affected (optic nerve atrophy, Garner, 1976).

In addition to ocular impairment and blindness, the most common manifestations of onchocerciasis are skin-related, ranging from severe itching ("troublesome itch", which can disturb sleeping and working patterns) and papular onchodermatitis (acute and chronic) to skin lichenification and inflammation ("orange skin") and depigmentation ("leopard skin"), and in cases of lymphatic involvement also leading to "hanging groin" (Bradley, Whitworth & Basáñez, 2005).

Onchocerciasis is also associated with neuro-hormonal disorders, hypo-sexual dwarfism (Nakalanga syndrome), Nodding syndrome and epilepsy (Föger *et al.*, 2017; Hotterbeekx *et al.*, 2019). Fig. 1.1 provides a schematic representation of the lifecycle of *O. volvulus* and illustrations of onchocerciasis clinical manifestations.

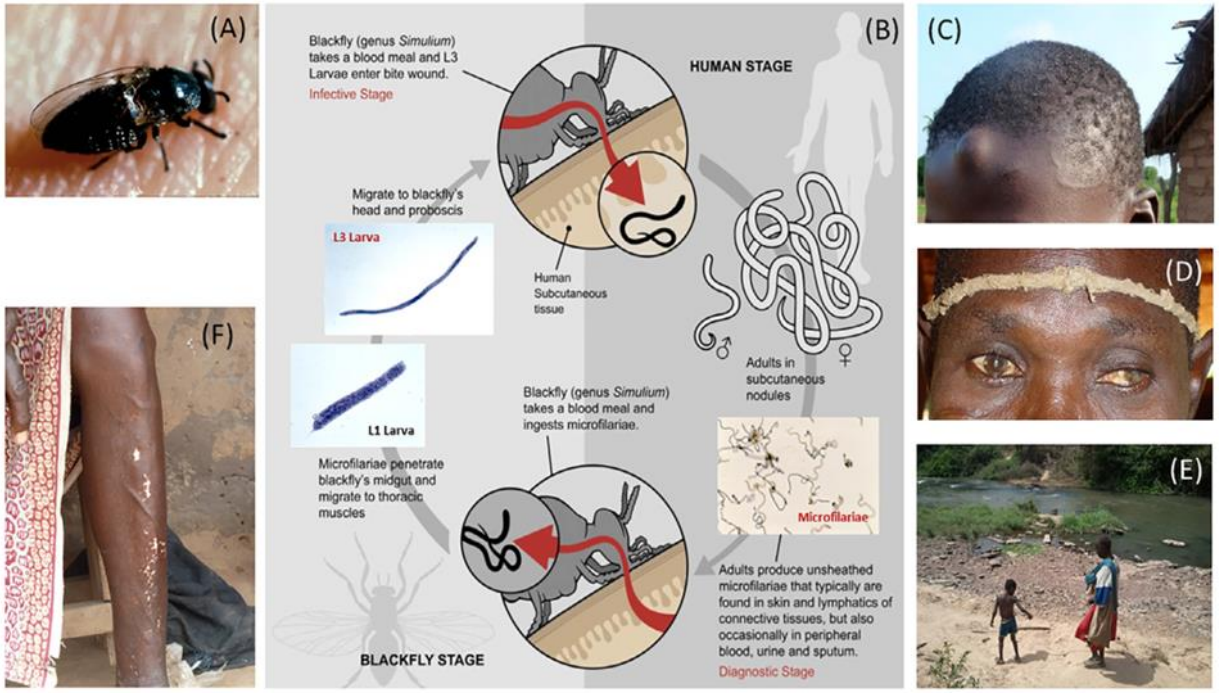


Fig. 1 (A) Vector (female *Simulium damnosum s.l.*) and (B) life cycle of *Onchocerca volvulus*; (C–F) disease manifestations associated with onchocerciasis: (C) head nodule in a child; (D) chronic uveitis with secondary cataract in right eye and sclerosing keratitis in left eye; (E) child leading a blind man; (F) skin depigmentation in the shin (leopard skin). In addition to skin and eye disease, onchocerciasis is also associated with human excess mortality and epilepsy (Colebunders et al., 2019; Little et al., 2004b; Walker et al., 2012). *Credits: (A) Rolf Garms; (B) Basáñez et al. (2006) for life cycle and Maria-Gloria Basáñez for microfilariae, L1 larva and L3 larva; (C, F) Simon J. O'Hanlon; (D) Adrian D. Hopkins; (E) Poppy H.L. Lamberton.*

Figure 1.1 – Lifecycle of *O. volvulus* and clinical manifestations of onchocerciasis (Cheke *et al*., 2021).

1.4 Diagnostics and Infection Metrics

Typically, infection prevalence is measured by the proportion of those individuals examined who are positive for skin microfilariae. Infection intensity is measured by the microfilarial load, i.e., the number of microfilariae per milligram of skin or per skin snip. Taking skin biopsies and incubating them in appropriate media for emergence and enumeration of microfilariae under a microscope is the gold standard diagnostic (Prost & Prod'hon, 1978), referred to as skin snip microscopy.

The prevalence of palpable nodules (nodule prevalence) is measured by the proportion of examined individuals with palpable onchocercomas. Nodule prevalence, measured in samples of 50 adult males, has been correlated with microfilarial prevalence (in those aged five or more years) to generate a rapid epidemiological assessment (REA) method used in the rapid epidemiological

mapping of onchocerciasis (REMO) (Coffeng et al., 2013a). Although this method is useful for assessing pre-control onchocerciasis endemicity, it is less suitable for monitoring and evaluating interventions (Duerr, Raddatz & Eichner, 2008).

Serological surveys to measure the prevalence of IgG antibodies against the Ov16 antigen of *O. volvulus* are used to assess changes in exposure indicative of EoT (World Health Organization, 2016). Detection of infection in blackfly samples is used for xeno-monitoring purposes during control programmes, often by the Poolscreen method (Katholi & Unnasch, 2006).

1.5 Control Interventions

The first large-scale control programme in West Africa was based on anti-vectorial measures by weekly aerial application of larvicidal insecticides in the breeding sites of the simuliid vectors, located in fast-flowing rivers (Dadzie, Neira & Hopkins, 2003). This was known as the Onchocerciasis Control Programme in West Africa (OCP, 1974–2002), which aimed at onchocerciasis elimination as a public health problem (EPHP) in 1.2 million square kilometres of land and protected 30 million at-risk people (Basáñez *et al.*, 2006). After 14 years of vector control (VC), the core OCP area was deemed free from blinding onchocerciasis (Hougard *et al.*, 2001). The OCP covered 11 endemic countries in West Africa and introduced the distribution of the endectocide ivermectin in the late 1980s to complement VC or as the sole measure in some foci of its Western Extension (Boatin, 2008). Ivermectin (Mectizan®) has been donated since 1987 by Merck & Co. Inc. to endemic nations as long as needed (Dadzie, Neira & Hopkins, 2003).

The African Programme for Onchocerciasis Control (APOC, 1995–2015) covered the 20 remaining endemic countries in the continent based on mass drug administration (MDA) of ivermectin, under the modality of annual community-directed treatment with ivermectin (CDTI) and averted 17.4 million DALYs (Coffeng et al., 2013b). Initially conceived as a programme aiming at EPHP, in 2010, APOC launched a more ambitious conceptual framework for onchocerciasis EoT by CDTI (World Health Organization/African Programme for Onchocerciasis Control, 2010). In 2015, at the closure of APOC, control and elimination efforts were devolved to the Ministries of Health of the affected countries with technical support by the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) (Colebunders *et al.*, 2018). Before its closure, APOC held a series of consultation meetings and prepared a report on alternative treatment strategies (ATS) to accelerate

onchocerciasis EoT (World Health Organization/African Programme for Onchocerciasis Control, 2015).

1.6 Effects of ivermectin on *O. volvulus*

The main impact of the drug is the microfilaricidal effect, clearing 98–99% of the skin microfilariae in 1–2 months after treatment (Basáñez *et al.*, 2008). Ivermectin also has an embryostatic effect, temporarily interrupting microfilariae production by the adult worms for several months (NTD Modelling Consortium Onchocerciasis Group, 2019; Basáñez et al., 2008). In addition, it is thought that ivermectin exerts a cumulative irreversible effect on microfilarial production (Plaisier et al., 1995) and a moderate macrofilaricidal effect (Walker *et al.*, 2017a). The feasibility of EoT by ivermectin CDTI is strongly dependent on the level of initial endemicity (pre-control microfilarial prevalence and intensity), indicative of the intensity of transmission by blackfly vectors (Stolk *et al.*, 2015; Walker *et al.*, 2017b; NTD Modelling Consortium Onchocerciasis Group, 2019).

Due to the long lifespan of the adult worms and the lack of a potent macrofilaricidal effect of ivermectin, MDA treatment must be continued for prolonged periods to help reach EoT (Burnham, 1998; World Health Organization, 2016). The WHO has indicated that the minimum therapeutic coverage (the proportion of the total population treated) should reach at least 65% of the total population and 80% for EoT, with a 100% geographical coverage (the proportion of at-risk villages that are covered by treatment) (World Health Organization, 2016).

1.7 Regional Goals

In Africa, some countries are expected to reach EoT by 2030, such as Togo and Malawi (Burki, 2021; Basáñez *et al.*, 2019). Other African countries, such as Cameroon, the Democratic Republic of the Congo (DRC) and Angola, are unlikely to achieve this goal (Burki, 2021), partly because Cameroon and the DRC are highly endemic, and partly because they are also co-endemic with *Loa loa*, another filarial nematode causative of loiasis (and transmitted by tabanid, *Chrysops* flies). Ivermectin treatment of those with heavy *L. loa* microfilarial load can lead to severe adverse events

(SAEs), including fatalities, precluding the use of classical CDTI, particularly in hypoendemic areas (Gardon *et al.*, 1997; Blok *et al.*, 2021)[1].

Once onchocerciasis EoT is achieved and confirmed by O-150 PCR in blackflies using the Poolscreen algorithm (Katholi & Unnasch, 2006), with <0.1% of infective flies, and Ov16 IgG4 test in children under ten years of age, with <0.1% seropositivity (World Health Organization, 2016; Cama *et al.*, 2018), post-treatment surveillance (PTS) is carried out for three years or until strong evidence confirms that transmission has been permanently eliminated in the country (World Health Organization, 2016). Even after reaching EoT, continued efforts will be necessary to prevent the re-introduction and re-establishment of the parasite in the population by post-elimination surveillance (PES) until the risk of resurgence ceases to exist in the neighbouring countries (World Health Organization, 2016).

1.8 Mathematical Modelling

Two onchocerciasis transmission models have been used to inform the WHO NTD 2021–2030 goals, namely EPIONCHO-IBM (and its deterministic EPIONCHO version) and ONCHOSIM (Basáñez *et al.*, 2016; Coffeng *et al*., 2014; NTD Modelling Consortium Onchocerciasis Group, 2019; Walker *et al*., 2017b). Both EPIONCHO-IBM and ONCHOSIM are stochastic, individual-based models, with the former being developed at Imperial College London (London, United Kingdom) and the latter at Erasmus Medical Center (Rotterdam, The Netherlands). According to a joint comparison of the outputs of both models, EoT would be feasible in low-moderate endemic areas with long-term MDA at high therapeutic coverage (≥75%), but more uncertain in highly endemic areas, those with poor coverage and adherence, or those where MDA has not yet, or only recently, started. The models indicate that highly endemic settings would benefit from switching to biannual (or quarterly) MDA and implementing VC where possible (among other alternative strategies). For this project, EPIONCHO-IBM was used (see Methods for a summary description of the model) (Hamley *et al.*, 2019).

[1] In onchocerciasis hyperendemic areas which are loiasis co-endemic, it is thought that the benefits of CDTI outweigh the risks of SAEs, whilst the opposite is true in hypoendemic areas.

1.9 Togo and History of Control

The Togolese Republic is a West African country located between Ghana, Burkina Faso and Benin and shares the coastline with the Atlantic Ocean in the South (Fig. 1.2). Togo is divided into five regions, from North to South: Savanes, Kara, Centrale, Plateaux and Maritime (Fig. 1.2). The latter region is where the capital, Lomé, is situated, holding 1.9 million in the metropolitan area of the country's nearly 8.3 million inhabitants (Worldmeters/United Nations, 2021; World Urbanization Prospects (United Nations), 2021).

Despite a growing economy, the nation is one of the poorest in the world (Mati *et al.*, 2018), with most of its population working on agriculture and over 50% living below the poverty line in 2017 (The World Bank, 2020). Some of the most fertile agricultural soils are found near rivers, where blackflies breed (Dadzie, Neira & Hopkins, 2003). Hence, by eliminating the parasite from the region, new agricultural land would become available to promote the Togolese economy (Dadzie, Neira & Hopkins, 2003; Norgbey, 1997).

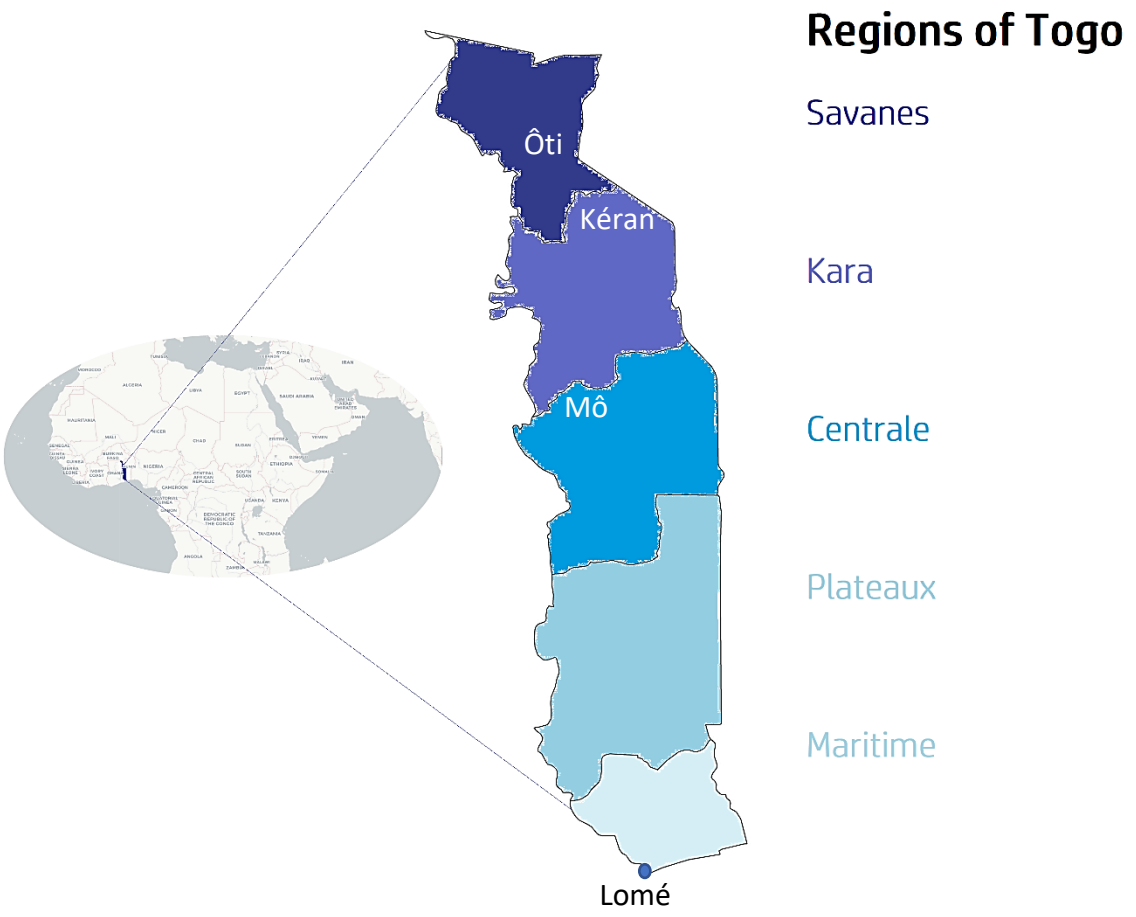


Figure 1.2 — Map of the five regions of Togo and its location in West Africa.

Although the bulk of illnesses and the leading causes of death in Togo are pathogen-related (Adaptation Fund, 2018), substantial efforts have been made to improve the health of its population. The nation was the first sub-Saharan country to reach EPHP of African trypanosomiasis (sleeping sickness) (World Health Organization, 2020a) and lymphatic filariasis (elephantiasis) (World Health Organization, 2017). The Togolese Ministry of Health (MoH) aims to reach EoT of onchocerciasis, in agreement with the WHO NTD roadmap for 2021–2030 (World Health Organization, 2020c). At baseline, before any intervention, the country encompassed onchocerciasis foci ranging from hypoendemic (<30% microfilarial prevalence) to holoendemic (≥80% microfilarial prevalence).

Togo has numerous river basins and tributaries. The northern and central regions are particularly challenging to achieve EoT due to the blackfly-prolific river basins of Kéran, Mô and Ôti and nearby hard-to-reach villages (Fig. 1.2) (World Health Organization/African Programme for Onchocerciasis Control, 2006).

Most of the Togo territory was part of the OCP (O'Hanlon *et al.*, 2016). The country was gradually covered by the programme (Fig. 1.3A), becoming part of Phase II (upper left corner of Savanes), Phase III East (rest of Savanes, Kara and upper part of Centrale), and Southern Extension (rest of Centrale, Plateaux and most of Maritime), beginning VC with aerial larviciding in January 1976, March 1977 and February 1988, respectively (O'Hanlon *et al.*, 2016). The Southern Extension was a necessary expansion of the OCP as it was a tangible source of *Simulium* reinvasion, threatening the effectiveness of VC (Dadzie, Neira & Hopkins, 2003). In 1989, ivermectin MDA started to be implemented in the OCP. Ivermectin MDA was initially delivered by mobile field teams, which could not achieve high geographical and therapeutic coverages (Komlan *et al.*, 2016). Eventually, CDTI was adopted with the aim of reaching and sustainably maintaining the required therapeutic coverage to achieve onchocerciasis EPHP (Boatin, 2008; Dadzie, Neira & Hopkins, 2003).

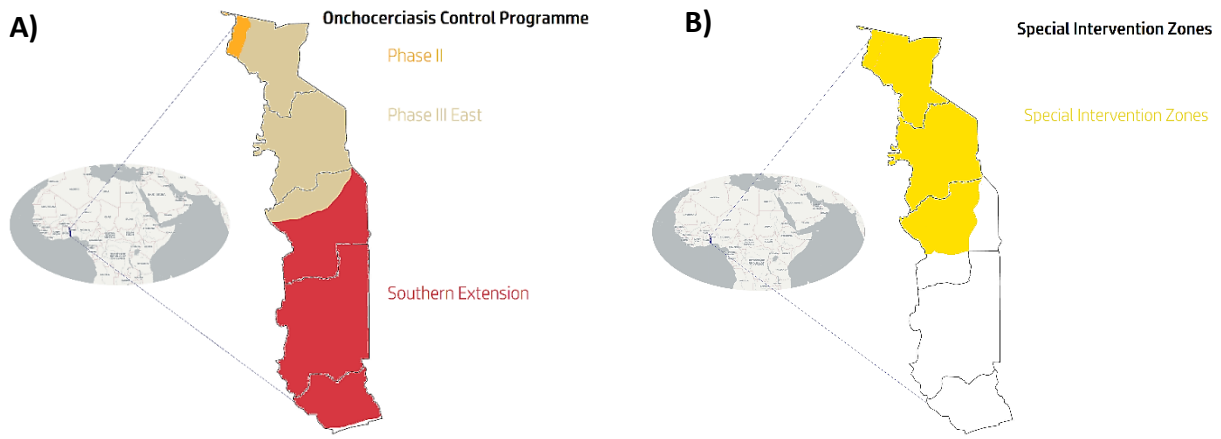


Figure 1.3 — Onchocerciasis control in Togo under the OCP (a) and SIZ (b).

After the closure of the OCP, some of Togo's persistent foci were covered by the so-called Special Intervention Zones (SIZ, 2002–2007; Fig. 1.3B) (Yaméogo, 2008; World Health Organization/African Programme for Onchocerciasis Control, 2002). These were created to strengthen control interventions post-OCP in foci where the EPHP goals were not fully met and transmission was ongoing. The SIZ covered villages from Savanes, Kara and Centrale regions (Fig. 1.2b), extending aerial VC and implementing biannual (twice-yearly) ivermectin MDA where justified, with high therapeutical coverage (around 85%, World Health Organization/African Programme for Onchocerciasis Control, 2006). Combined larviciding and ivermectin MDA substantially impact transmission, with reported reductions in annual transmission potential (ATP, the number of L3 larvae per person per year) of up to 90% after the first two years of intensified interventions (Dadzie, Neira & Hopkins, 2003). After the end of the OCP and SIZ, the Togolese MoH continued the delivery of ivermectin MDA through annual CDTI (Komlan *et al.*, 2016).

1.10 Aims and Objectives

The current project aims at understanding the temporal and spatial trends of *O. volvulus* infection in Togo under the control interventions implemented from 1976 to 2019 to assess the current epidemiological situation and the prospects of EoT by 2030. Such aim is given by the commitment of the Togolese MoH to achieve onchocerciasis EoT by 2030, and a collaboration agreement that had been put in place between the onchocerciasis modelling groups of the NTD Modelling Consortium (at Imperial College London and Erasmus Medical Center), Health & Development International Inc. (HDI), and the Togolese MoH. Specifically, the project objectives are:

(1) to calibrate EPIONCHO-IBM for the various epidemiological settings of Togo according to region and history of control;
(2) to generate temporal and spatial infection trends;
(3) to identify foci that may have reached EoT and may start stop-MDA surveys;
(4) to identify foci that may require complementary intervention strategies, designated alternative treatment strategies (ATS, e.g. increased treatment frequency or coverage; focal VC; alternative treatments) to achieve EoT by 2030.

2. Methods

2.1 EPIONCHO-IBM model

EPIONCHO-IBM follows every human in a closed population, tracking the number of infecting microfilariae and infecting adult *O. volvulus* (by sex and reproductive status). Infection with male and female worms is necessary to produce microfilariae, assuming a polygamous mating system (Schulz-Key & Karam, 1986). The model accounts for exposure of humans to blackfly bites at an age- and sex-dependent level (Filipe *et al.*, 2005) whilst also integrating individual variation in exposure (Hamley *et al.*, 2019). Mortality rates of microfilariae and adult worms rise with the age of the parasite (known as senescence). The model is stochastic for the number of adult worms and the number of microfilariae per milligram of skin in each individual.

Density-dependent processes regulating parasite abundance in vectors and humans are assumed to govern in three stages of *O. volvulus* lifecycle: a) establishment of ingested microfilariae within the simuliid vector (leading to a saturation curve describing the relationship between L3 larvae and microfilariae ingested per fly parameterised for savannah vector–parasite combinations (Basáñez, Churcher & Grillet, 2009); b) parasite-induced mortality of the vector (whose rate increases linearly with the number of ingested microfilariae); and c) establishment of adult worms within the human host (which decreases non-linearly with transmission intensity as measured by the ATP (Basáñez & Boussinesq, 1999).

As for the mating probability of adult worms (the probability that a female worm is fertilised by a male), it is assumed that the worms are polygamous and that the presence of a male is sufficient to mate all females in an individual (Hamley *et al.*, 2019). Fertile and fertilized female worms produce microfilariae. The number of microfilariae produced by fertile female worms is reduced through age. The lifespan of the adult worms was set at ten years and microfilariae at 15 months (Hamley *et al.*, 2019).

The model considers a latent period in the development of the parasite within the vector by including the L1, L2 and L3 larvae stages, based on data for African settings, and models deterministically the dynamics of the parasite inside the vector are at a blackfly population level (Walker *et al.*, 2017b). The lifespan is set as 3.5 days for L3 larvae and two weeks for blackflies.

Treatment with ivermectin is presumed to exert a large but finite microfilaricidal effect which reduces with time since treatment (following the dynamics presented in Basáñez et al., 2008). As described in section 1.6, it is also assumed that ivermectin temporarily sterilises some female worms (embryostatic effect) whilst making others permanently infertile (cumulative sterilising effect) (Plaisier *et al.*, 1995). VC has a relative impact on reducing the annual biting rate (ABR), that is, the number of bites per person and per year. A complete description and mathematical definition of EPIONCHO-IBM is presented in (Hamley *et al.*, 2019; Walker *et al.*, 2020).

The model was calibrated and run for three different levels of control interventions classified as "optimistic", "reference/standard" and "pessimistic" scenarios, defined in section 2.3; and four endemicity levels characterised by microfilarial prevalence of 30% (hypoendemic), 50% (mesoendemic), 70% (hyperendemic) and 90% (holoendemic). An additional intervention scenario with 100% efficacy of VC for the duration of anti-vectorial measures was also explored following Plaisier *et al.*, 1997.

To reach these target prevalence levels, the ABR's were calibrated (by interpolating from the EPIONCHO-IBM's relationship between microfilarial prevalence and ABR presented in Hamley *et al.* (2019) as 290, 615, 2,200 and 60,000 blackfly bites received per person per year for hypoendemicity, mesoendemicity, hyperendemicity and holoendemicity, respectively. Villages recorded with baseline (pre-control) information were distributed across these four endemicity levels with a 10% variation. For example, a village with a 35% initial endemicity prevalence would be inserted into the 30% microfilarial prevalence scenario, with simulation comprising pre-control endemicities ranging from 20% to 39.9% microfilarial prevalence.

According to the three levels of control interventions and four endemicities defined in the previous paragraphs, 12 different scenarios were conducted for each region and SIZ status for a standard village of 500 individuals. Each scenario was simulated 100 times for microfilarial prevalence over the years. The average behaviour of the simulations was extracted and plotted, with the results of the optimistic and pessimistic scenarios used as the lower and upper uncertainty bounds**,** respectively**,** for the reference outputs. The simulations covered the epidemiological situations in Togo from 1970 to 2030, assuming that the ivermectin MDA intervention is not interrupted after commencing.

2.2 Data Sources

This project involved the compilation of two databases containing geographical, epidemiological and historical control information on VC and ivermectin MDA. The data were obtained from the OCP (EPICROSS) database and progress reports (World Health Organization/Onchocerciasis Control Programme in West Africa, 2000, 2001a, 2001b)), SIZ reports, MoH of Togo reports (TOGO MOH), World Health Organization and Expanded Special Project for Elimination of Neglected Tropical Diseases (WHO-ESPEN), as well as from publications by Komlan *et al.* (2016); Korbmacher *et al*. (2018); Hill *et al*. (2019); Noma *et al.* (2014); Biritwum *et al*. (1997). The data cleaning and exploratory analysis were performed using R (R Core Team, 2021) and RStudio (RStudio Team, 2021), using the computer cluster at the Imperial Research Computing service (Imperial College Research Computing Service, 2021).

2.3 Proposed Scenarios of VC Efficacy, MDA Coverage and Treatment Compliance

Based on the data provided by the Togolese MoH, three control scenarios were defined to run the EPIONCHO-IBM model (Table 2.1). These scenarios assume three distinct inputs: VC efficacy, MDA therapeutical coverage, and probability of non-compliance (PNC, percentage of the population that never receives ivermectin). The optimistic scenario assumes a 90% VC efficacy and an increasing MDA coverage, reaching the 80% suggested by the WHO to achieve EoT (World Health Organization, 2016). Although the efficacy of VC has been deemed to have exceeded 90% in several regions of the OCP (Hougard *et al.*, 2001), there are settings in which it was lower, such as in the mountain region of Oti (Boatin *et al.*, 1997). The reference and pessimistic models assume 75% and 60% VC efficacy, respectively (Table 2.1).

The PNC is set at 1% for the optimistic simulations, as it tends to be lower for high therapeutic coverages (Krentel, Fischer & Weil, 2013; Babu & Kar, 2004; Senyonjo *et al.*, 2016) and is increased to 2.5% and 5% for the reference and pessimistic scenarios, respectively, according to Turner et al., 2013 (Table 2.1). The MDA therapeutic coverage was moderately low during the first years of scale-up (1991 to 1995) (Boatin, 2008). Afterwards, CDTI aimed for at least 65% coverage during the remaining period of the OCP to achieve EPHP (1996 to 2001), followed by a coverage of 80% for EoT (2002 to date) (World Health Organization/African Programme for Onchocerciasis Control, 2010, 2006). Based on this information, Table 2.1 presents the proposed MDA coverage levels for the three scenarios over the years.

When justified, simulations with 100% VC efficacy were also run for the three MDA coverages scenarios. Naturally, these scenarios are not distinguishable until the start of ivermectin MDA.

Table 2.1 — Control scenarios proposed for the Togo history of control simulations regarding VC efficacy, MDA therapeutic coverage, and proportion of systematic non-compliance (PNC).

Scenario	VC Efficacy %	MDA Coverage 1991-1995 %	MDA Coverage 1996-2001 %	MDA Coverage 2002-2030 %	PNC %
Optimistic	90%	65%	75%	80%	1.0%
Reference/ Standard	75%	50%	65%	75%	2.5%
Pessimistic	60%	50%	65%	65%	5.0%

2.4 Data Cleaning & Preparation

All variables utilised were at the village level apart from the beginning of ivermectin MDA, which was only available at the district level for 35 districts, including the sub-district of Mô. The surveyed villages belong to 33 of the 35 districts (Table 2.2, no villages surveyed from Akébou and Vou). There are currently 36 districts in Togo, as Tône district was recently split into Cinkassé and Tône (Dorkenoo *et al.*, 2018; Direction Générale de la Statistique et de la Comptabilité Nationale (République Togolaise), 2017; République du Togo, 2011). Variables with missing values were completed as much as possible by searching other data sources. The start of the VC variable was 15.7% incomplete and was complemented according to the river basin nearest to the village in question. It was assumed that the start of VC coincides in all surrounding villages of a particular river basin (O'Hanlon *et al.*, 2016).

Vo and Akébou districts do not have any village surveys (Table 2.2), despite representing 6.4% of the Togolese rural population. Vo has been considered free from onchocerciasis since 2006 (World Health Organization & African Programme for Onchocerciasis Control, 2006), as currently four other Maritime districts (END in Africa, 2016). As for Akébou, the district is presently under CDTI (Ministere de la Sante et de la Protection Sociale, 2015), and surveillance data will be necessary to define its endemicity level.

Table 2.2 — Distribution and level of endemicity of surveyed villages across Togo districts and regions. The population data were obtained from République du Togo (2011).

District	Villages Surveyed (number)	Endemicity number of villages				Togo Overall Population %	Togo Rural Population %
		Hypoendemic	Mesoendemic	Hyperendemic	No Baseline		
Region of Savanes						**13.4%**	**18.4%**
Cinkassé	Previously part of Tône					1.3%	1.3%
Kpendjal	11	2	1	1	9	2.5%	3.9%
Oti	29	1	1	-	27	3.1%	4.3%
Tandjoare	2	-	-	-	2	1.9%	3.0%
Tône	4	-	1	-	3	4.6%	5.9%
Region of Kara						**12.4%**	**15.2%**
Assoli	2	1	-	-	1	0.8%	0.9%
Bassar	21	-	2	2	17	1.9%	2.5%
Binah	1	-	-	-	1	1.1%	1.7%
Dankpen	21	1	1	-	19	2.1%	3.1%
Doufelgou	4	-	2	-	-	1.3%	1.5%
Kéran	19	-	1	2	16	1.5%	2.1%
Kozah	26	-	1	1	24	3.7%	3.4%
Region of Centrale						**10.0%**	**12.1%**
Blitta	32	7	8	5	12	2.2%	3.3%
Mô	8	-	-	-	8	0.6%	1.0%

Sotoubou a	29	3	12	-	14	2.0%	2.5%
Tchamba	13	2	7	-	4	2.1%	2.8%
Tchaoudjo	9	1	-	2	6	3.1%	2.5%
District	**Villages Surveyed** (number)	**Endemicity** number of villages	**Togo Population** %	**Togo Rural Population** %	**District**	**Villages Surveyed** (number)	**Endemicity** number of villages
Region of Plateaux						**22.2%**	**28.6%**
Agou	16	3	-	1	12	1.4%	2.1%
Akébou	0	-	-	-	-	1.0%	1.4%
Amou	10	-	1	1	8	1.7%	2.6%
Anié	14	3	3	2	6	1.5%	1.5%
Danyi	6	1	2	-	3	0.6%	0.9%
Est-mono	21	4	6	5	6	2.0%	3.0%
Haho	23	4	4	2	13	4.0%	5.5%
Kloto	7	2	-	1	4	2.3%	1.7%
Kpele	1	-	1	-	-	1.2%	1.8%
Moyen-mono	9	1	3	4	1	1.2%	1.8%
Ogou	35	1	5	9	20	3.7%	4.0%
Wawa	13	1	1	2	9	1.6%	2.3%
Region of Maritime						**42.0%**	**25.7%**
Avé	4	-	-	-	4	1.6%	2.4%
Bas-Mono	2	-	-	-	2	1.4%	2.1%
Golfe	1	-	-	-	1	25.3%	2.4%
Lacs	1	1	-	-	-	2.8%	3.8%
Vo	0	-	-	-	-	3.4%	5.0%
Yoto	23	1	-	1	21	2.7%	3.7%
Zio	10	2	-	-	8	4.8%	6.3%

Although Maritime is by a considerable margin the most populated region in Togo, the bulk of its population resides in urban areas (Table 2.3). The region with the largest rural population is Plateaux (Table 2.3), whereas Savanes is the most rural. As a disease that burdens villages near rivers, onchocerciasis is related to the rural population and the size of the villages, and it is anticipated to be negatively correlated to the urbanisation level (Goldstein, 1990; Saker *et al.*, 2004). Hence, a decision had been made to select for ivermectin MDA only those villages with ≤ 2,000 inhabitants, where the risk of the disease was considered higher according to the drug donation policy by Merck & Co. Inc. (USAID, 2019). A systematic review of all Togolese villages is in place since 2019 to ensure that all at-risk villages are treated independently of the population size (USAID, 2019).

The distribution of the Togolese population between 2011 and 2021 across its five regions can be compared between Table 2.2 and Table 2.3. Nowadays, Savanes holds a smaller fraction, as opposed to Plateaux. This difference seems to be linked to the size of the territory, as Savanes is the smallest region and Plateaux the largest.

Table 2.3 — Size and regional distribution of surveyed Togolese villages.

Region of Togo	Villages surveyed Number of villages (proportion)	Population size of the villages surveyed Mean inhabitants (min-max)*	Togo population distributed in each region % (Dietz, 2021)	Rural population in of each Togolese region % (République du Togo, 2011)
Savanes	49 (11.4%)	334 (57-1332)	11.9%	85.9%
Kara	91 (21.3%)	259 (34-861)	12.1%	76.0%
Centrale	94 (22.0%)	296 (57-1027)	10.0%	75.4%
Plateaux	151 (35.3%)	273 (43-721)	23.6%	80.3%
Maritime	43 (10.0%)	185 (42-517)	42.4%	38.1%
Overall	428 (100.0%)	273 (34-1332)	100.0%	62.3%

* min-max — minimum and maximum.

After harmonising villages with different spellings (e.g., "Amouta" and "Ammouta", "Fétigbé" and "Fetigbe"), and spacing ("Amouta " and "Amouta"), duplicated surveys were removed if these coincided with respect to village name, river basin name, year of survey, number of people examined by skin snip, number of positive people by skin snip, and crude prevalence. Lastly, it was confirmed that all villages were assigned to a region of Togo, and those lacking information on the region were allocated to one using maps or through a literature search.

VC requires some years to strongly influence prevalence values (Hougard *et al.*, 2001) as opposed to the immediate impact of ivermectin on microfilarial levels. Hence, and following O'Hanlon *et al*. (2016), villages with prevalence surveys taken before the first ivermectin MDA and no more than two years after VC commencement were considered to have their baseline (pre-control) endemicity recorded. For the establishment of the pre-control prevalence variable, two other variables were required. Firstly, a variable for the difference between the year of the prevalence survey and the start of VC. Secondly, a variable for the difference between the year of the prevalence survey and the start of ivermectin MDA. Any survey with a value of two or less in the first variable and no more than zero in the second variable was considered a baseline prevalence survey. Ninety-five per cent confidence intervals (95% CIs) for the crude prevalence for each survey were calculated using the Wilson binomial score (Brown, Cai & DasGupta, 2001).

There was information on crude prevalence and standardised prevalence. Standardised prevalence was age- and sex-adjusted according to the OCP reference population (Moreau, Prost & Prod'hon, 1978), and it would have been preferable to use it (Kirkwood, 1988). However, the standardised prevalence variable had 11.7% missing values, particularly from recent surveys, in contrast with only 1.2% for crude prevalence. To evaluate the comparability of the two variables, the linear relationship between the two was investigated (Fig. 2.1), with a Pearson's correlation coefficient of 0.99. Therefore, the crude prevalence was used for subsequent analysis.

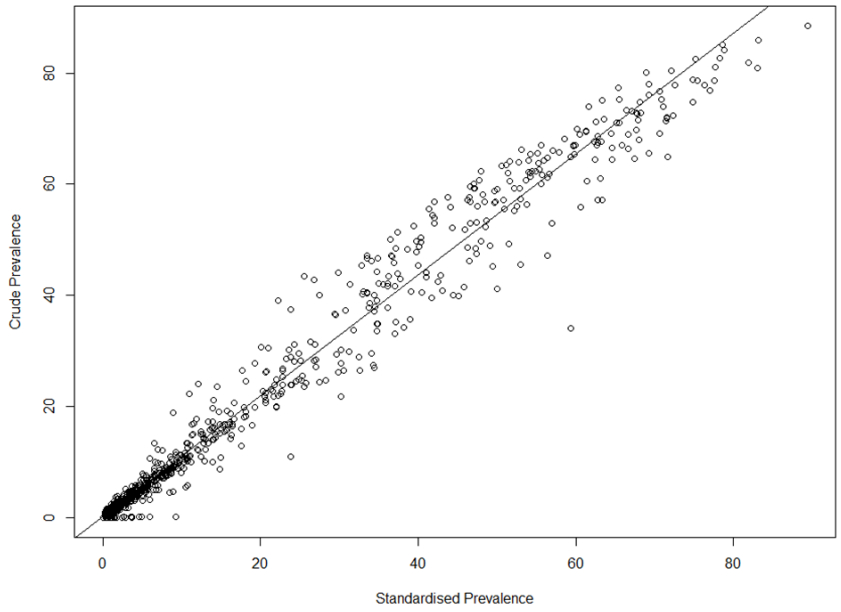


Figure 2.1 — Linear relationship between crude microfilarial prevalence and standardised microfilarial prevalence.

2.5 Exploratory data analysis

2.5.1 OCP phases, SIZ and start of control

Onchocerciasis prevalence surveys in Togo began in 1975 at the village level within the OCP and were available until 2017 for this study. Onchocerciasis control during the OCP was gradually implemented in Togo from North to South, firstly with aerial VC and since 1989 with ivermectin MDA (Table 2.4). While many of the endemic villages of Savanes and Kara were included in the programme during Phase III East, a considerable part of Centrale was only covered in the later Southern Extension phase. Plateaux and Maritime were also incorporated into the Southern Extension, besides a small area of Plateaux, included in Phase II and aimed to eliminate the Djodji form of *Simulium sanctipauli* (Cheke *et al.*, 2008), a more competent vector for *O. volvulus* (Garms *et al.*, 1988; Cheke & Denke, 1988). In this area, VC ceased in 1989, when the Djodji form was believed to have been eliminated and became extinct (Cheke *et al.*, 2008; Lamberton *et al*., 2014; O'Hanlon *et al.*, 2016).

Table 2.4 — History of OCP implementation and control interventions (VC and ivermectin MDA) in the Togolese regions at the village level.

OCP phase	Villages covered by the OCP by region % (number)					Start year of VC year	Start year of ivermectin MDA Median year (min-max)*
	Savanes	Kara	Centrale	Plateaux	Maritime		
Phase II	8.2% (4)	–	–	0.7% (1)	–	1976	1993 (1993-1993)
Phase III East	89.8% (44)	85.7% (78)	20.2% (19)	–	–	1977	1991 (1988-2000)
Southern Extension	2.0% (1)	14.3% (13)	79.8% (75)	99.3% (150)	100.0% (43)	1988-89	1991 (1988-1995)
Special Intervention Zones	88.9% (43)	87.7% (79)	16.0% (15)	0.0% (0)	0.0% (0)	-	-

* min-max — minimum and maximum.

The SIZ in Togo was mostly circumscribed to Savanes and Kara regions but included some villages in Centrale (Table 2.2). Villages selected for the SIZ still had high onchocerciasis prevalence at the closure of the OCP in 2002 (Fig. 2.2). The additional control of the SIZ villages reduced prevalence to levels comparable to those in the non-SIZ villages by 2007 (Fig. 2.3A versus Fig. 2.3B, respectively). Fig. 2.2 depicts some villages with higher prevalence after 2010 compared to previous years. Most of these villages were part of the SIZ, suggesting that, without the VC implemented during OCP and SIZ, the low prevalence is no longer sustained, and ATS may be needed to achieve EoT in such settings.

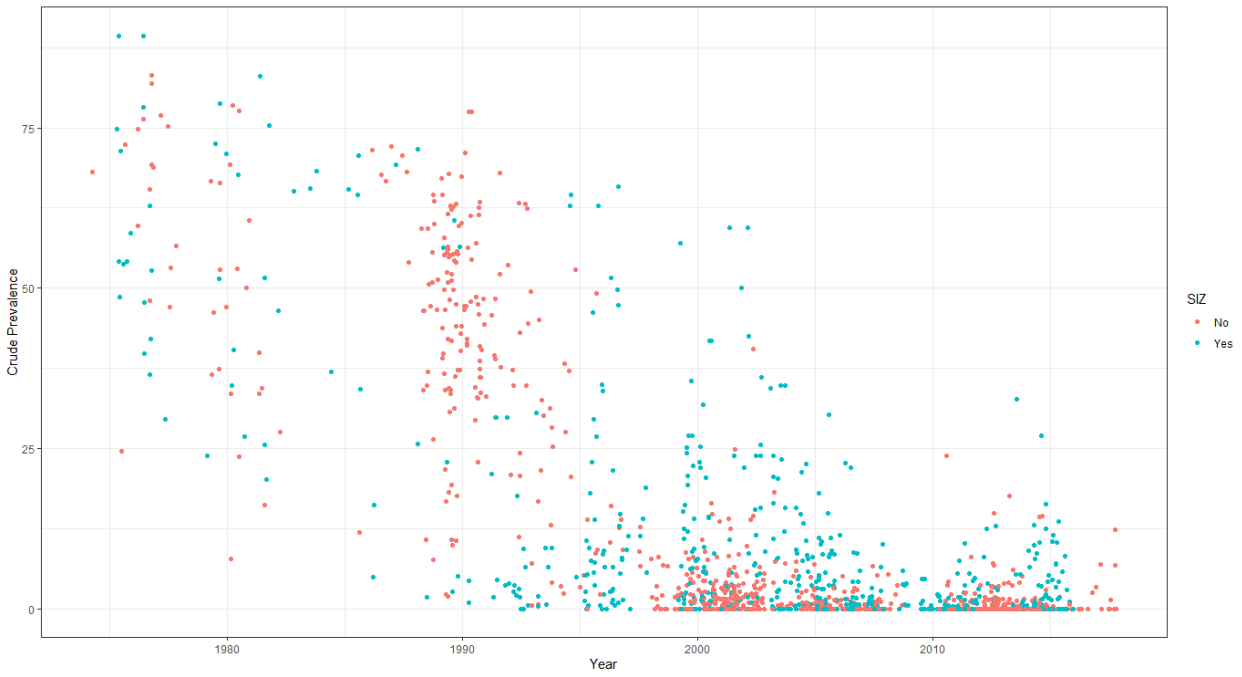


Figure 2.2 — Crude microfilarial prevalence in SIZ and non-SIZ villages.

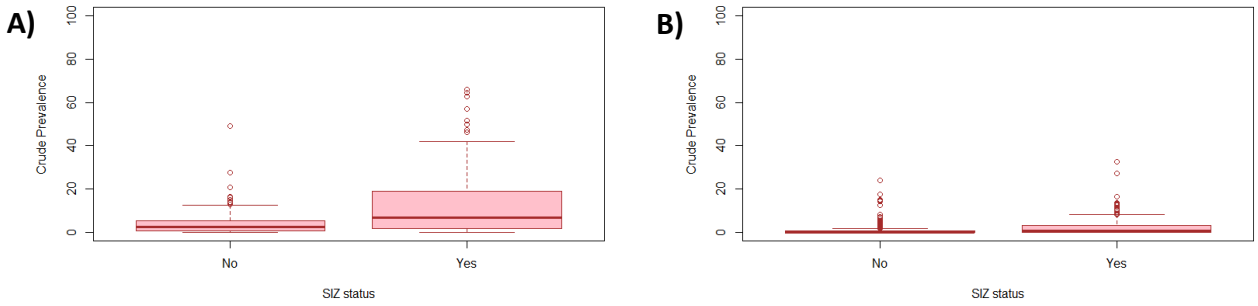


Figure 2.3 — Crude microfilarial prevalence in SIZ (yes) and non-SIZ (no) villages between **(A)** 1995 and 2001, and **(B)** 2007 and 2017. Median (horizontal dark red line), 25th-75th percentiles (pink rectangle), 1.5 times the interquartile range (vertical dashed dark red lines) and outlier values (white dots).

2.5.2 Proportion of the population surveyed per village over time

There was a significant negative linear relationship between the proportion of the population surveyed per village and the survey year (linear regression p-value < 2e-16). On average, the proportion of the village population surveyed per year decreased by 0.5% (95% CI 0.4% - 0.6%). For instance, over 80% of the population was examined for skin microfilariae at the beginning of the OCP, which dropped to below 70% between 2006 and 2015 (Fig. 2.4), the decade with smaller prevalence (Fig. 2.2). The reduction in the proportion of the population tested may denote a failure to test certain population groups that may have been absent at the time of examination (e.g.,

fishermen and gold prospectors, World Health Organization/African Programme for Onchocerciasis Control, 2006) or an increased reluctance of the population to present at the parasitological examination by skin snip microscopy, as taking skin snips is a mildly invasive procedure.

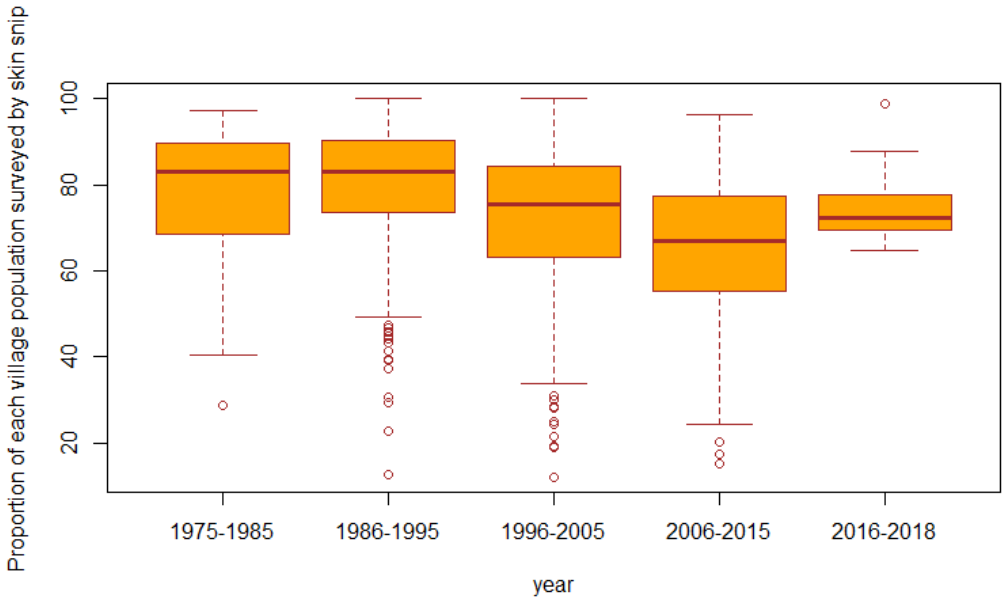


Figure 2.4 — Relationship between the proportion of the population surveyed in each village and the year of the survey. Median (horizontal dark red line), 25th-75th percentile (orange rectangle) 1.5 times the interquartile range (vertical dashed dark red lines) and outlier values (white dots).

2.5.3 Model Inputs: Duration of VC and ivermectin MDA start for each region and SIZ status in Togo

The duration of the control vector was defined for each region and SIZ and non-SIZ (Table 2.5). The SIZ regions had more years of VC. Distribution of ivermectin began in 1989 in the OCP region, and in 1991 most villages in Togo with baseline prevalence started MDA (Table 2.6)[2]. Based on the data and to compare the model outputs of those of the EPIONCHO-IBM model with the ONCHOSIM *(*Melchers, 2021), the MDA start was set *at* 1991 (Table 2.5).

Table 2.5 — Input values of control interventions for each region and SIZ status of Togo.

Input variable	**Region** year				
	Savanes	Kara	Centrale	Plateaux	Maritime

[2] Table I in the Appendix provides information of all villages' MDA start, regardless of baseline prevalence.

	Non-SIZ	SIZ	Non-SIZ	SIZ	Non-SIZ	SIZ		
VC start	1977	1977	1989	1977	1989	1977	1989	1988
VC end	1994	1993	2002	2007	2002	2007	2002	2002
MDA start	1991							

Table 2.6 — Year of MDA start for each region and SIZ status of Togo with baseline prevalence surveys.

Year of MDA start year	**Region** % villages								**Nationwide** % villages
	Savanes		Kara		Centrale		Plateaux	Maritime	
	Non-SIZ	SIZ	Non-SIZ	SIZ	Non-SIZ	SIZ			
1988	-	25.0%	-	81.8%	-	100.0 %	-	-	7.4%
1991	-	-	-	-	100.0 %	-	64.4%	16.7%	63.1%
1992	-	-	-	9.1%	-	-	27.4%	-	14.1%

2.5.4 Onchocerciasis endemicity levels through time in Togo

Onchocerciasis crude microfilarial prevalence in Togo was plotted since the start of the OCP to illustrate epidemiological trends of infection over time for villages with recorded baseline microfilarial prevalence (Fig. 2.5) and villages that entered the programme but in which baseline prevalence had not been recorded (Fig. 2.6). The data were organised into three levels of pre-control prevalence: hypoendemic (<40% microfilarial prevalence), mesoendemic (40% to 59%) and hyperendemic (≥60% microfilarial prevalence) (adapted from Prost, Hervouet & Thylefors (1979) and NTD Modelling Consortium Onchocerciasis Group (2019)). Subsequently, the villages were

distributed according to the five regions of Togo and SIZ status. Most villages included in the SIZ (88%) did not have a recorded baseline prevalence, in contrast to half of the non-SIZ villages (56%). The VC duration and ivermectin MDA start for the plots were extracted from Table 2.5 and Table 2.6 for the villages with recorded baseline endemicity and Table 2.5 and Table I from Appendix I for villages lacking this information.

Most villages with information on pre-control prevalence from Savanes, all from Kara and one from Centrale were part of the SIZ. They had variable levels of endemicity (Fig. 2.5B, C, E, respectively), even between the same levels of baseline prevalence, indicating different levels of effectiveness of interventions. In contrast, the non-SIZ villages with recorded pre-control endemicity from Savanes had high prevalence (mesoendemic and hyperendemic; Fig. 2.5A), which had decreased to very low levels (95% CIs <5.0%) by the end of VC but before the start of ivermectin MDA. This suggests that VC was effective and valuable in controlling transmission. A similar situation of effective interventions may be observed with Centrale non-SIZ (Fig. 2.5D), whose endemicity is less than 15% since 1997 due to VC and MDA. Plateaux has villages with all levels of endemicity (Fig. 2.5F), from 2.0% (95% CI 0.8% to 6.4%) to 83.2% (95% CI 77.8% to 87.6%). Control interventions seem to have been successful in this region, reducing microfilarial prevalence over time. Maritime has fewer surveys (Fig. 2.5G), mostly with low endemicity. Control interventions substantially reduced the prevalence of infection in the region.

As for villages without recorded baseline prevalence (Fig. 2.6), Savanes and Maritime seem to be close to attaining regional EoT (Fig. 2.6A, B, H), while Plateaux may need a few more years of ivermectin MDA (Fig. 2.6G). Centrale and Kara have varying prevalence, with some settings increasing since the end of VC (Fig. 2.6C, D, E, F).

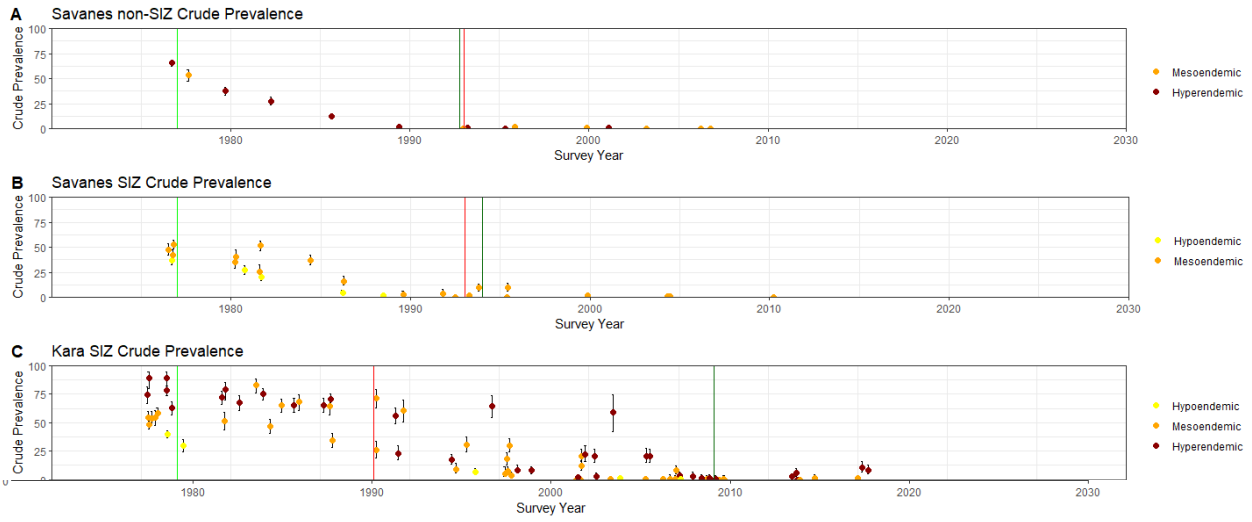
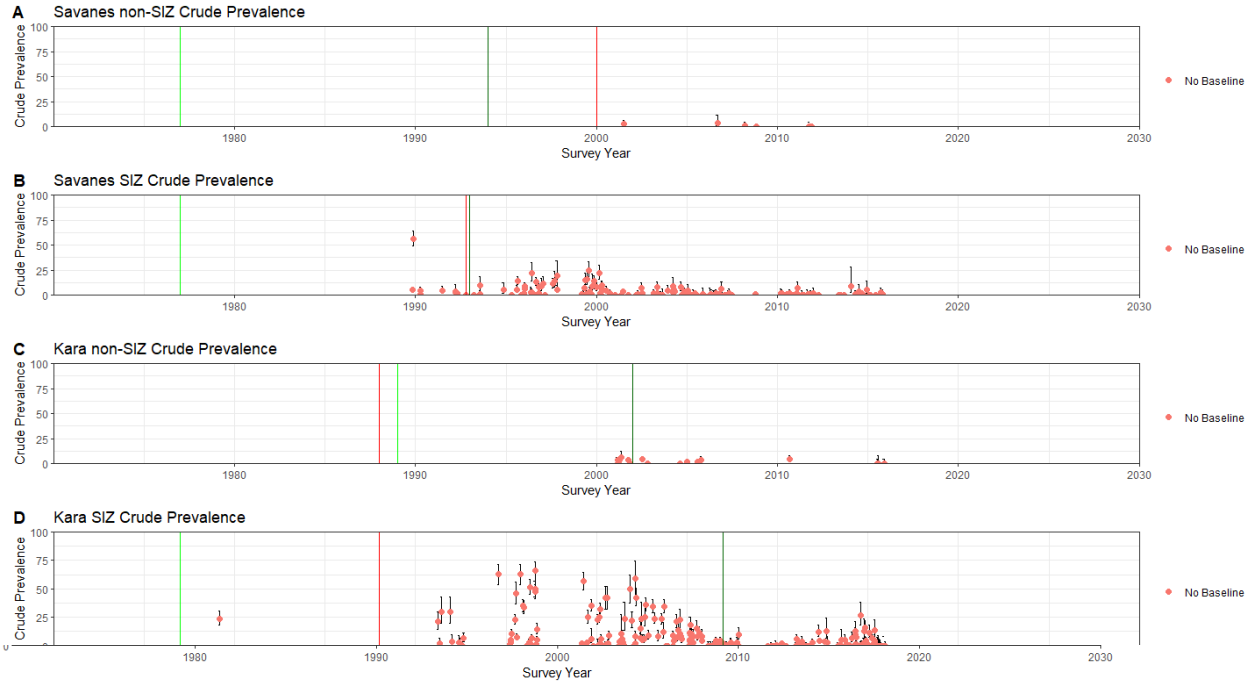


Figure 2.5 — Onchocerciasis endemicity levels (hypoendemic; mesoendemic; hyperendemic) in Togo over time for each region and SIZ status in villages with recorded baseline endemicity. Vertical lines denote start of VC (light green line); end of VC (dark green line) and start of MDA (red line). The dots are village surveys, with colours denoting hypoendemicity (yellow), mesoendemicity (orange) and hyperendemicity (dark red). The error bars are 95% CIs calculated by Wilson binomial scores.



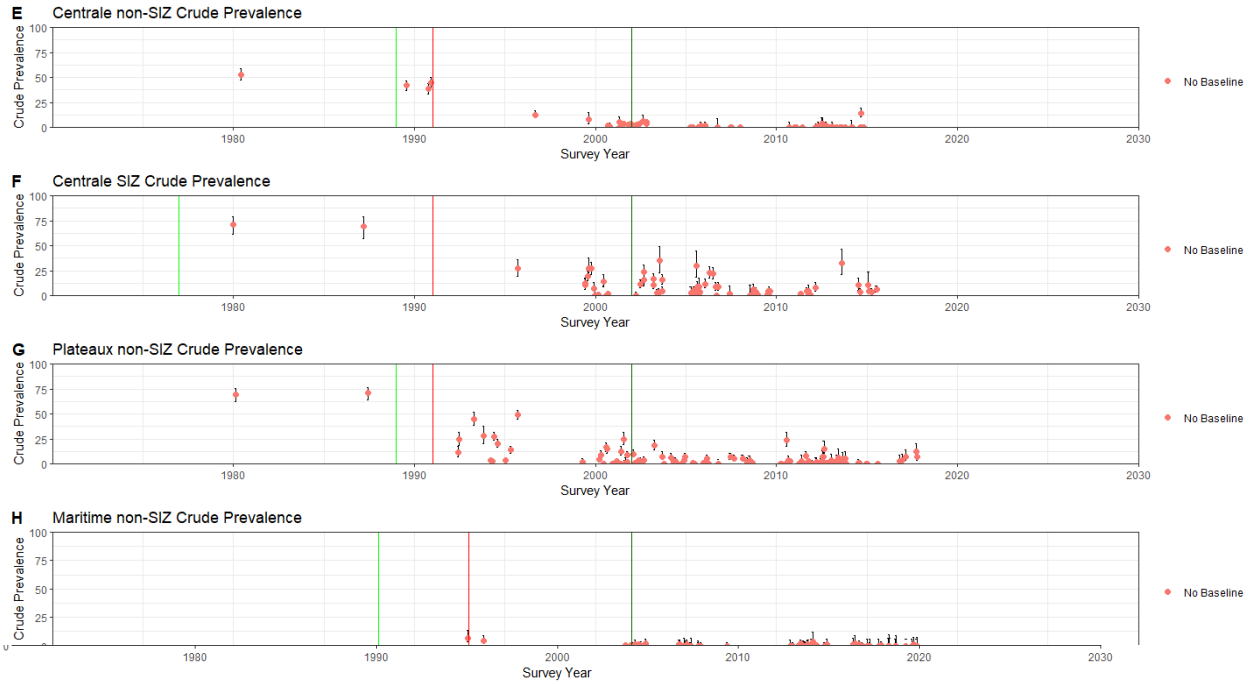


Figure 2.6 — Onchocerciasis surveys from villages without recorded baseline endemicity in Togo over time for each region and SIZ status. Vertical lines denote start of VC (light green line); end of VC (dark green line) and start of ivermectin MDA (red line). The dots are village surveys, and the error bars are 95% CIs calculated by Wilson binomial scores.

3. Results

The EPIONCHO-IBM model outputs are described below at the region and SIZ status levels for the villages with recorded pre-control endemicity (section 3.1). The results for the villages where baseline endemicity information was lacking can be found in Appendix II. The outputs are analysed and compared with the data from the villages.

3.1 Villages with recorded baseline endemicity

There are no surveys from villages with information on baseline endemicity in Kara non-SIZ. As such, the discussion of results in the region will involve Kara SIZ and Kara non-SIZ in villages without recorded baseline prevalence information.

3.1.1 Savanes non-SIZ

Savanes non-SIZ has data for two simulated pre-control endemicity levels: 50% and 70% microfilarial prevalence (Fig. 3.1). In the 50% simulations, one village has temporal trends of microfilarial prevalence best captured by the optimistic simulation (Fig. 3.1A). The impact of VC was substantial in controlling the transmission of the disease, although it probably did not reach 100% (Fig.3.1B). After the end of VC, ivermectin MDA appears to be sufficient to protect the gains accrued through VC, possibly leading to EoT. This village could be selected for stop-MDA surveys.

For the hyperendemic village, the simulation results that capture the data best are those that assume 100% VC efficacy (Fig. 3.1 D). Probably, this village lies between mesoendemicity and hyperendemicity (Fig. 3.1D, E). The difference in prevalence between the first survey, in 1977, and the second in 1980, is 28%. This reduction is too fast to be due to VC. Moreover, excluding the first and last surveys, the village follows the 50% prevalence scenario with 100% VC efficacy (Fig. 3.1D), suggesting, like in the previous statement, that VC had a tangible impact on Savanes.

The first survey of the hyperendemic community is distinctly hyperendemic, and the last poll still has a small prevalence. This village is the one with the most citizens in the dataset. Although the community size grew over the years (from 967 to more than 1,300), fewer people were examined over time. In particular, the first survey examined 760 inhabitants in 1977, and the last one, in 2001, only approached 171. As such, recent surveys may be missing groups exposed to the disease. Overall, this settlement resembles hyperendemicity and the simulations assuming baseline 70%

microfilarial prevalence suggest that EoT has not been achieved and that ivermectin MDA and ATS should be implemented.

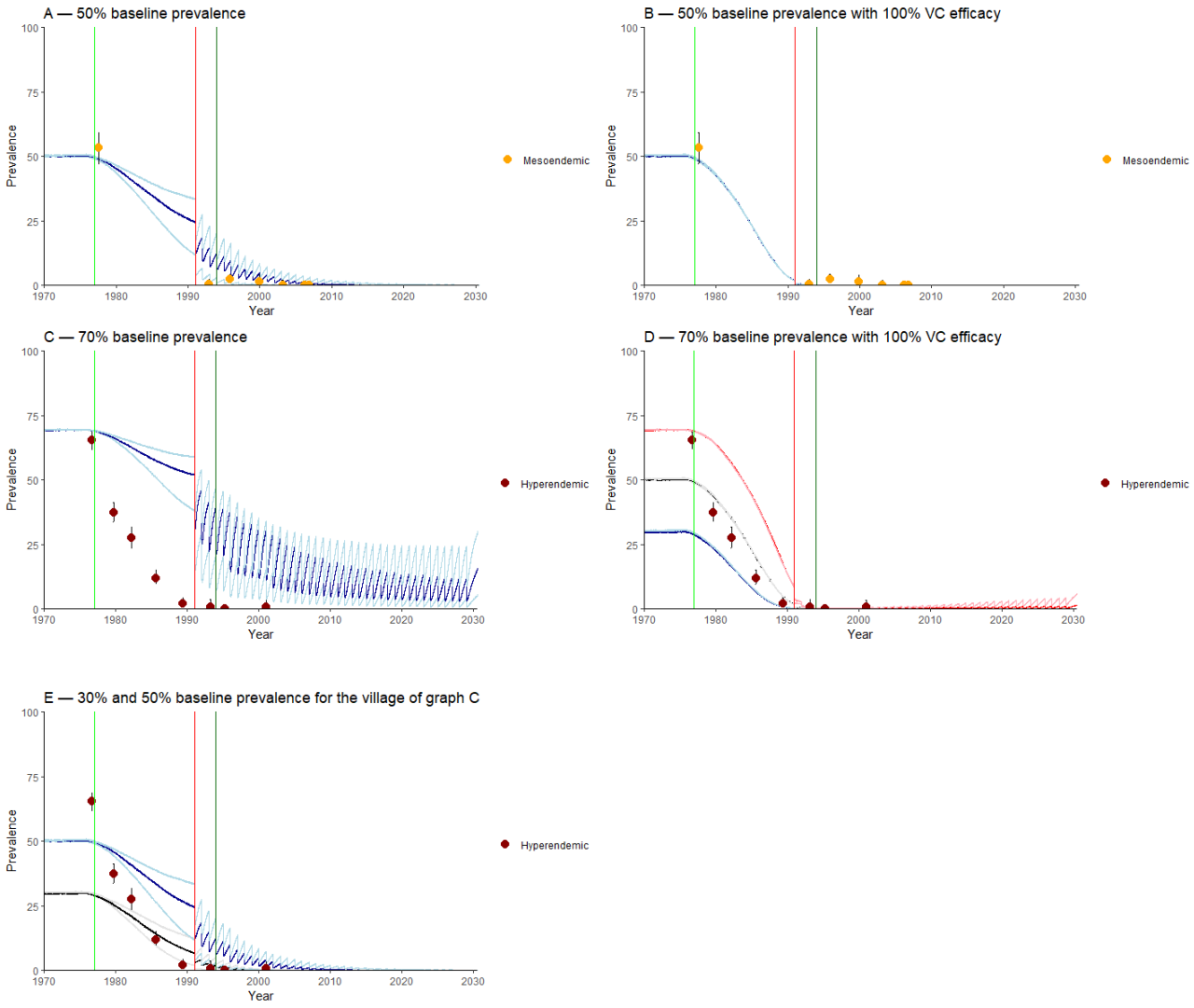


Figure 3.1 — Model outcomes for Savanes non-SIZ with available pre-control endemic prevalence. **(A)** Mesoendemic village and simulated 50% baseline prevalence; **(B)** Mesoendemic village and simulated 50% baseline prevalence with 100% VC efficacy; **(C)** Hyperendemic village and 70% baseline prevalence; **(D)** Hyperendemic village and 70% baseline prevalence with 100% VC efficacy; **(E)** Hyperendemic village with simulated 30% and 50% baseline. The village surveys are represented by orange (mesoendemic) or brown (hyperendemic) dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line) and start of ivermectin MDA (red line). Dark model output coloured lines (red, blue or black) indicate simulation results for the reference intervention scenario; light coloured lines (light blue, light red or grey) indicate simulation results for the pessimistic scenario (upper bound) or the optimistic scenario (lower bound)

3.1.2 Savanes SIZ

Savanes SIZ has data for two simulated pre-control endemicity levels: 30% and 50% (Fig. 3.2). The 30% simulations capture the data for one hypoendemic village well with the optimistic (Fig. 3.2A) and the 100% VC efficacy (Fig. 3.2B) scenarios, despite having an initial high hypoendemicity. Remarkably, VC impacted infection prevalence, almost reducing it to zero in the last survey (1.8% microfilarial prevalence, 95% CI 0.9% to 3.5%), before the start of MDA, supporting the outcome from the previous section that VC was very efficient on Savanes.

The three mesoendemic villages in the 50% simulations are diverse and broadly captured by the reference and optimistic intervention scenarios (Fig. 3.2C) and the 100% VC efficacy scenario (Fig 3.2D). More precisely, the community with the highest mesoendemicity (highest microfilarial prevalence survey in 1977, Fig. 3.2C) follows the reference scenario; the village with intermediate mesoendemicity (intermediate microfilarial prevalence survey in 1977, Fig. 3.2C) follows the optimistic scenario; and the centre with low mesoendemicity (lowest microfilarial prevalence survey in 1977, Fig. 3.2D) follows the situation with 100% VC efficacy.

These results support three statements. Firstly, pre-control prevalence greatly impacts the transmission dynamics of onchocerciasis, even among the same endemicity levels (i.e. high, intermediate or low mesoendemicity). Secondly, surveys do not mix between villages or scenarios, with the model capturing the data well. Furthermore, it implies that control interventions have had comparable impacts on the communities in the region, and baseline endemicity levels remain regular through time. Lastly, even the high mesoendemic village follows the reference scenario, with the other two communities following the optimistic and 100% VC efficacy simulations. These outcomes indicate an impactful VC and that ivermectin MDA was enough to the EoT in the mesoendemic settings of Savanes SIZ. Hence, stop-MDA surveys could be implemented in these villages.

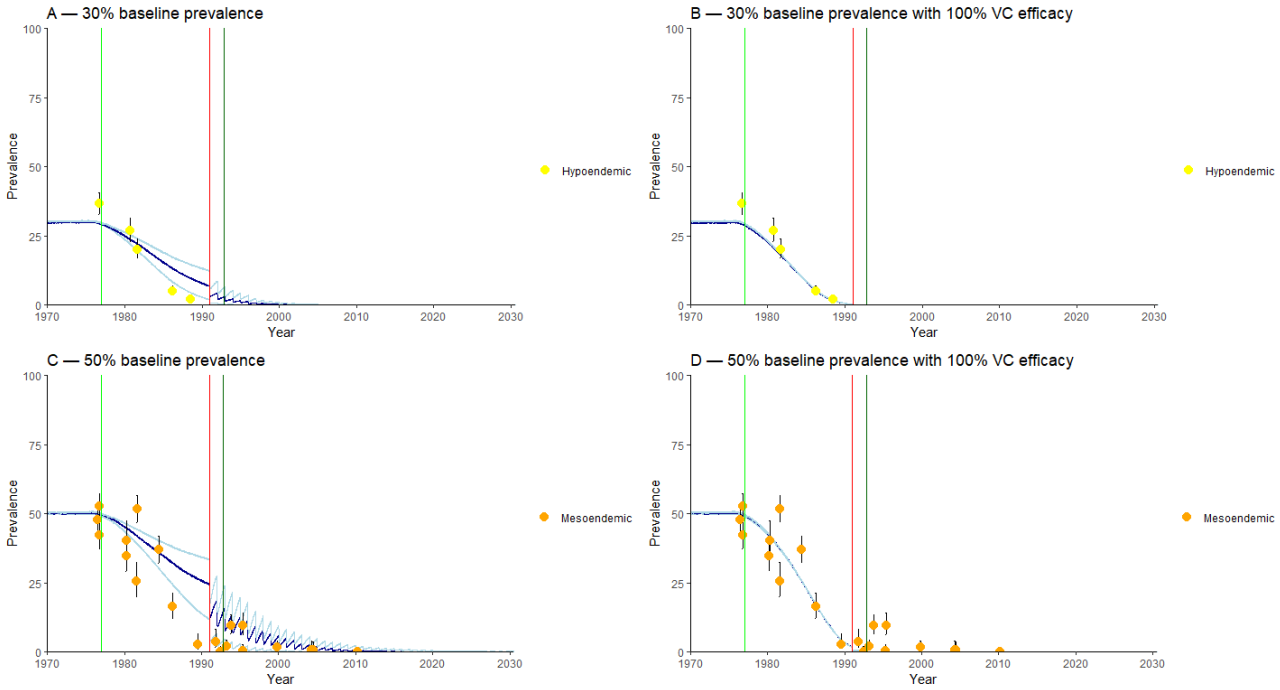


Figure 3.2 — Model outcomes for Savanes SIZ with available pre-control endemic prevalence. **(A)** Hypoendemic village and simulated 30% baseline prevalence; **(B)** Hypoendemic village and simulated 30% baseline prevalence with 100% VC efficacy; **(C)** Mesoendemic villages and simulated 50% baseline prevalence; **(D)** Mesoendemic villages and simulated 50% baseline prevalence with 100% VC efficacy. The village surveys are represented by yellow (hypoendemic) or orange (mesoendemic) dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line) and start of ivermectin MDA (red line). Dark model output coloured lines (blue) indicate simulation results for the reference intervention scenario; light coloured lines (light blue) indicate simulation results for the pessimistic scenario (upper bound) or the optimistic scenario (lower bound).

3.1.3 Kara SIZ

Kara SIZ has data for all the simulated pre-control endemicity levels: 30%, 50%, 70% and 90% (Fig. 3.3) and in this region VC continued until 2007. The 30% hypoendemic data seem to be best captured by the pessimistic scenario (Fig. 3.3A) and have reached EoT. It follows the pessimistic simulation, as the village pre-control endemicity is highly hypoendemicity and not likely because the interventions were less effective.

For the mesoendemic, initially introduced in 50% prevalence scenario (Fig. 3.3B), the temporal infection trends in some (arguably mesoendemic) villages are best reflected by the reference scenario, whilst two settings are better reflected by the outputs of the 70% endemic prevalence simulations, suggesting uncertainty in baseline endemic prevalence (Fig. 3.3E). Albeit the latter two communities have pre-control mesoendemic surveys, they rise to hyperendemicity during the first years of VC. These villages are relatively populated (300 to 600 inhabitants), and their number of

positive cases did not increase from 1977 to 1990; however, the number of people examined was much smaller. Accordingly, there may have been a selection of who should be tested, potentially as it was time-consuming and resource-intensive to investigate the entire community. All servers after 2010 are from these two communities. One of them seems to be of high mesoendemicity, achieving a null prevalence in the last survey. The other village has had a steady and very low prevalence since VC ended (95% CI from 0.4% to 4.5% microfilarial prevalence), and ATS should be implemented to ensure it reaches the EoT. Regarding the three mesoendemic villages that follow the 50% reference scenario, their prevalence is nil at the end of VC, and stop-MDA is endorsed. Stop-MDA is also recommended to the high mesoendemic village with no prevalence in the last survey.

For the 70% microfilarial prevalence simulations, there are three hyperendemic villages with high initial prevalence (Fig. 3.3C). They follow the pessimistic scenario until the start of ivermectin MDA, probably because they are slightly more endemic than the 70% simulations. Since ivermectin has been distributed, the prevalence has dropped substantially. In the end, one of the villages seems to have followed the optimistic scenario, having a null prevalence in the last survey. The other two villages have low but stable prevalence (95% CIs from 0.6% to 5.4% over the years). Temporal infection trends for the hyperendemic communities are broadly captured by the range of intervention scenarios assumed, with simulations projected to 2030 suggesting ongoing transmission that would need to be tackled by the implementation of ATS, as cessation of VC in 2007 is followed by predicted stabilization or increases of microfilarial prevalence under annual ivermectin MDA alone.

The previous situation is even more pronounced for the holoendemic villages with 90% microfilarial prevalence. Up to the cessation of VC in 2007, the data fall within the predicted trends for the reference and optimistic intervention scenarios, but from 2007 onwards, EPIONCHO-IBM predicts strong resilience to annual ivermectin MDA not reflected by the data (Fig. 3.3D). This difference may be due to the VC having had a lasting impact on the population of blackflies, either in its abundance or proportion of species with different abilities to transmit the parasite. In Fig. 3.3E, the villages included in Fig. 3.3B and 3.3D are plotted along with the 70% baseline scenario simulations, overall improving the agreement between observations and model outputs. Note that the holoendemic villages start to follow the 70% pessimistic scenario (Fig. 3.3E) after the cessation of VC.

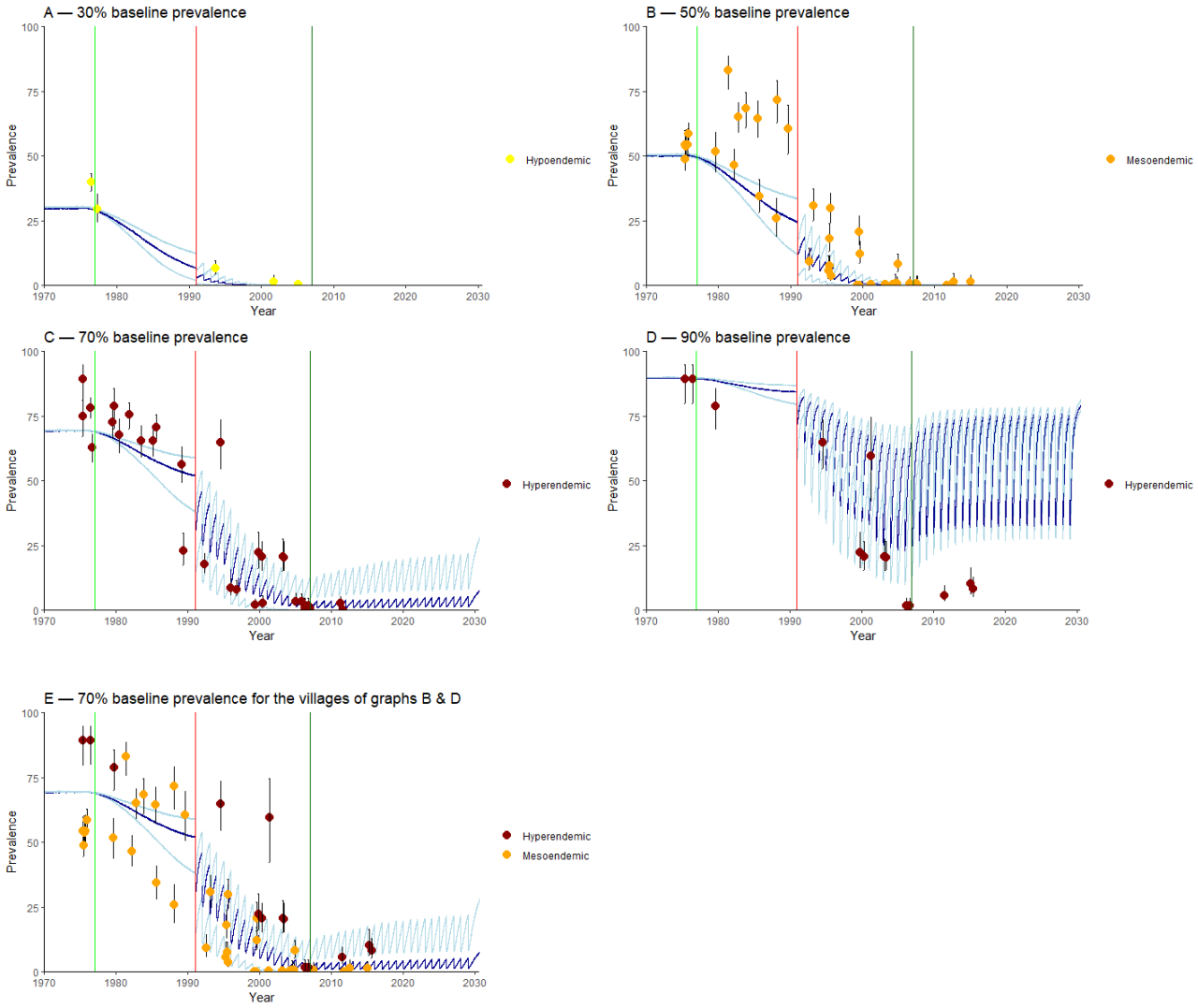


Figure 3.3 — Model outcomes for Kara SIZ with available pre-control endemic prevalence. **(A)** Hypoendemic villages and simulated 30% baseline prevalence; **(B)** Mesoendemic villages and simulated 50% baseline prevalence; **(C)** Hyperendemic villages and simulated 70% baseline prevalence; **(D)** Holoendemic villages and simulated 90% baseline prevalence; **(E)** Villages in (B) and (D) along the predicted microfilarial temporal dynamics for assumed 70% endemic prevalence. The village surveys are represented by yellow (hypoendemic), orange (mesoendemic) or brown (hyperendemic) dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line). Dark model output coloured lines (blue) indicate simulation results for the reference intervention scenario; light coloured lines (light blue) indicate simulation results for the pessimistic scenario (upper bound) or the optimistic scenario (lower bound).

3.1.4 Centrale non-SIZ

In the Centrale Non-SIZ villages, the maximum recorded baseline prevalence was about 70%, so the holoendemic prevalence scenario was not explored (Fig. 3.4). VC stopped in 2002, at the end of the OCP. Fig. 3.4B, with the 50% endemic prevalence simulations, tends to capture the hypoendemic and mesoendemic villages better than the 30% endemic prevalence simulations, suggesting again some uncertainty around the results of the parasitological surveys at baseline. Also, most of these communities are of high hypoendemicity or low mesoendemicity. There are no positive cases since 2010 in any of these villages, and they can proceed to stop-MDA surveys.

The temporal trends of both observed and predicted microfilarial prevalence for mesoendemicity are well-matched using the 50% baseline prevalence simulations (Fig. 3.4C), with model outputs predicting that EoT may be achieved and suggesting that these villages may be suitable for implementing stop-MDA surveys. The data comprises endemicities from low to high mesoendemicity, therefore matching all three scenarios (Fig. 3.4C). These villages last surveys did not have positive cases, apart from a centre with high mesoendemicity almost without prevalence and expected to reach it in the next few years.

The hyperendemic data for the 70% baseline prevalence simulations are best captured by the optimistic intervention scenario (Fig. 3.4D). Forward predictions indicate potential ongoing transmission and highlight the need to implement ATS to accelerate elimination. However, all surveys are of null prevalence since 2010. It is uncertain whether the villages have reached EoT or fewer people have been surveyed in the last decade, as the model suggests a small prevalence in the coming years. For instance, the Gnama-Gnama village examined 129 people in the first survey, but only 68 in the last poll, although its population has not decreased. These communities should proceed with stop-MDA surveys to explore If the prevalence remains nil.

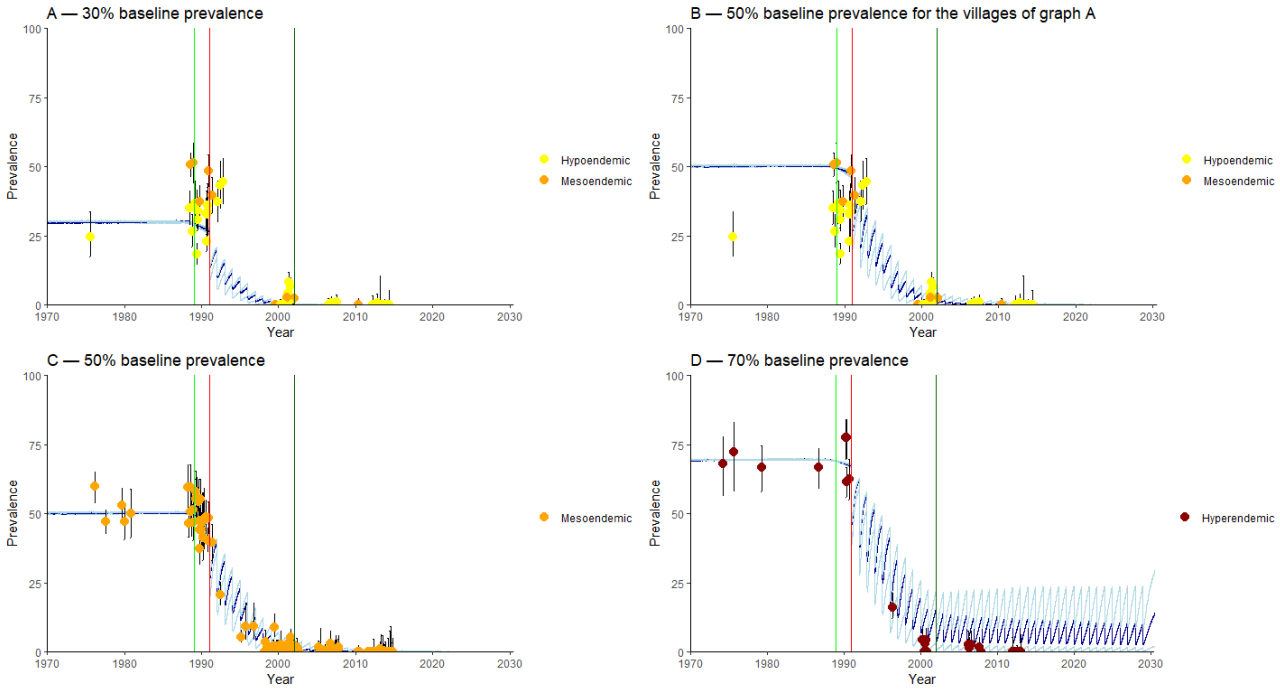


Figure 3.4 — Model outcomes for Centrale SIZ with available pre-control endemic prevalence. **(A)** Hypoendemic and low mesoendemic villages and simulated 30% baseline prevalence; **(B)** Hypoendemic and low mesoendemic villages and simulated 50% baseline prevalence; **(C)** Moderate and high mesoendemic villages and simulated 50% baseline prevalence; **(D)** Hyperendemic villages and simulated 70% baseline prevalence. The village surveys are represented by yellow (hypoendemic), orange (mesoendemic) or brown (hyperendemic) dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line). Dark model output coloured lines (blue) indicate simulation results for the reference intervention scenario; light coloured lines (light blue) indicate simulation results for the pessimistic scenario (upper bound) or the optimistic scenario (lower bound).

3.1.5 Centrale SIZ

The 70% endemic prevalence scenario captures the data for one hyperendemic village in Centrale SIZ within the predicted microfilarial temporal dynamics of the pessimistic intervention scenario (Fig. 3.5A). Both data and predictions suggest the need to implement ATS to achieve EoT, as annual ivermectin MDA does not appear to be sufficient. Although the community is part of SIZ, it is likely that it only had VC until 2002 instead of 2007, as it has been following the pessimistic simulation since then. Besides, there is substantial uncertainty around the baseline endemicity of the village as only a small percentage of the population has been examined in the pre-control survey.

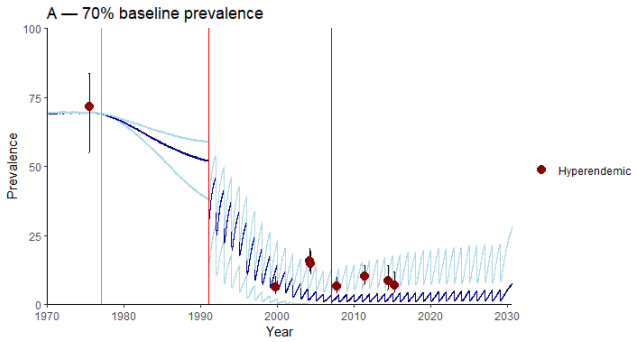


Figure 3.5 — Model outcomes for Centrale non-SIZ with available pre-control endemic prevalence. **(A)** Hyperendemic village and simulated 70% baseline prevalence. The village surveys are represented by brown (hyperendemic) dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line). Dark model output coloured lines (blue) indicate simulation results for the reference intervention scenario; light coloured lines (light blue) indicate simulation results for the pessimistic scenario (upper bound) or the optimistic scenario (lower bound).

3.1.6 Plateaux

For the Plateaux region, not included in SIZ, survey data with recorded baseline microfilarial prevalence exist for the 30%, 50%, and 70% endemicity scenarios (Fig. 3.6). Although simulations assuming 30% or 50% endemic prevalence tend to capture initial infection trends in hypoendemic communities, around the assumed year of termination of VC (2002), most of the observed prevalence trends are higher than predicted trends, suggesting, among other reasons, that VC may have ended earlier, or that initial endemicity levels may have been underestimated (Fig. 3.6A, B). Therefore, these data are also plotted along with the 70% endemic prevalence simulations in Fig. 3.6 C. Most villages better reflect the 50% pessimistic (Fig. 3.6B) situation, and most no longer have positive cases on the last surveys. There are still two villages with low prevalence in 2014 (0.7% and 1.5% microfilarial prevalence, with 95% CIs from 0.2% to 8.0%), which should reach EoT in the coming years, as the 50% pessimistic model suggests. Overall, hypoendemic villages achieved EoT in recent years, and the ones with vestigial prevalence should reach it by 2025. Stop-MDA surveys are endorsed after a few rounds of MDA.

A similar situation is depicted in Fig. 3.6D and E for the mesoendemic villages, whose infection trends may be better captured by the 70% prevalence simulation scenario. Most of these communities agree with the 50% endemic prevalence simulations (Fig. 3.6D), reaching EoT before 2020. The few settings that better fit the 70% simulations (Fig. 3.6E) will need ATS to attain EoT and may be hyperendemic at the baseline.

The data for the 70% endemic prevalence scenario seem to follow the trends predicted by the optimistic intervention scenario (Fig. 3.6F) or the pessimistic scenario with 100% efficacious VC (Fig. 3.6G). Predicted trends suggest that annual ivermectin MDA may not be sufficient to achieve EoT when assuming 70% initial endemic prevalence. However, most recent surveys are of null prevalence, and the size of the population examined has not decreased over time.

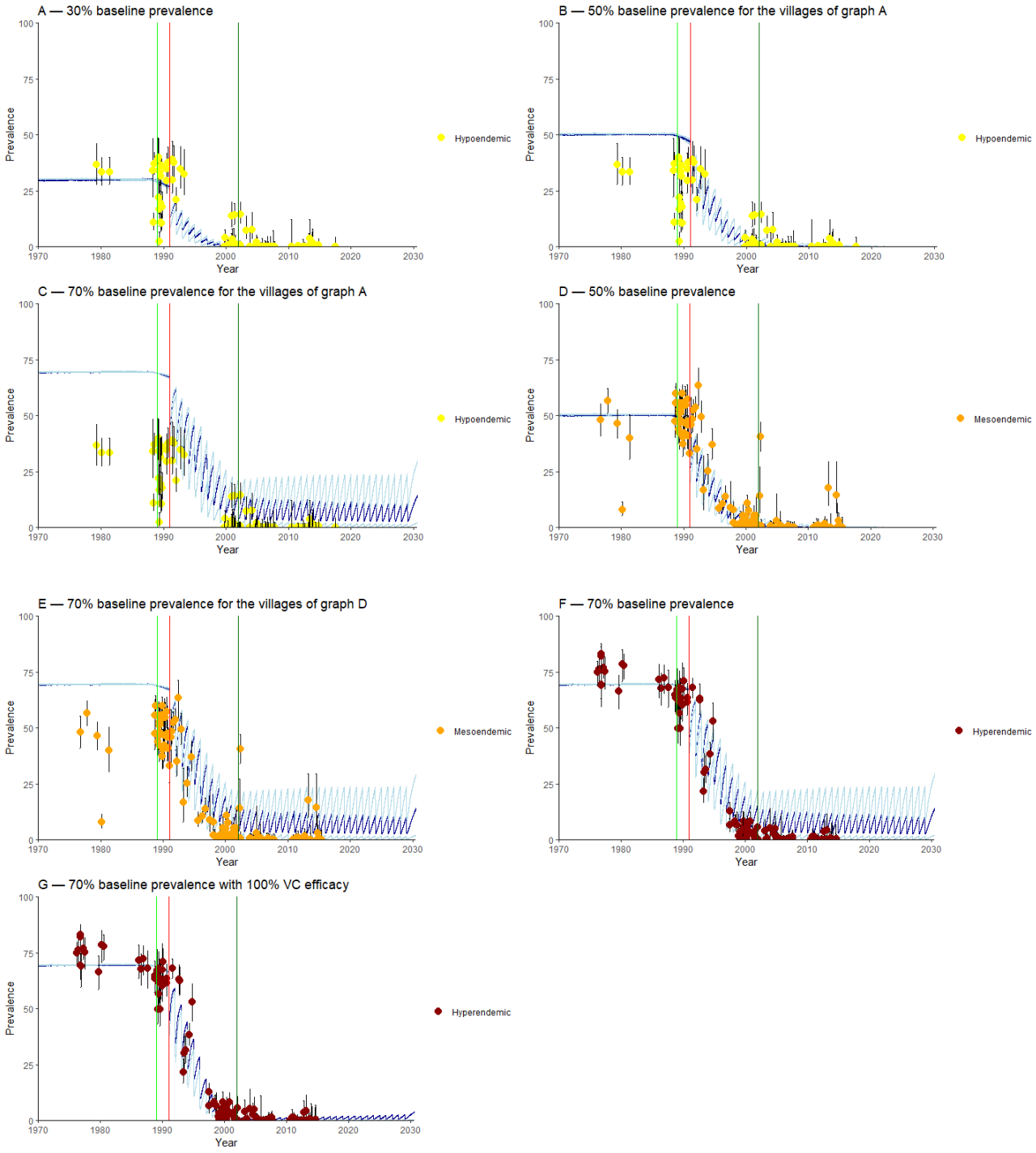


Figure 3.6 — Model outcomes for Plateaux with available pre-control endemic prevalence. **(A)** Hypoendemic villages and simulated 30% baseline prevalence; **(B)** Hypoendemic villages and simulated 50% baseline prevalence; **(C)** Hypoendemic villages and simulated 70% baseline prevalence; Mesoendemic villages and simulated 50% baseline prevalence; **(D)** Mesoendemic villages and simulated 50% baseline prevalence; **(E)** Mesoendemic villages and 70% baseline prevalence; **(F)** Hyperendemic villages and 70% baseline prevalence; **(G)** Hyperendemic villages and 70% baseline prevalence with 100% VC efficacy. The village surveys are represented by yellow (hypoendemic), orange (mesoendemic) or brown (hyperendemic) dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line). Dark model output coloured lines (blue) indicate simulation results for the reference intervention scenario; light coloured lines (light blue) indicate simulation results for the pessimistic scenario (upper bound) or the optimistic scenario (lower bound).

3.1.7 Maritime

Maritime has data available for the simulated endemicity levels of 30%, 50% and 70% (Fig. 3.7). Villages of relatively low hypoendemicity were plotted within the 30% endemic simulations (Fig. 3.7A). These communities are of moderate to very low hypoendemicity (Fig. 3.7A), following the 30% reference scenario and reaching zero prevalence by 2002.

The surveys for one hyperendemic village are broadly consistent with the reference intervention scenario with 50% endemic prevalence (Fig. 3.7B) simulation and not with the 70% prevalence scenarios (Fig. 3.7C). The village is on edge between mesoendemicity and hyperendemicity, with nil prevalence in its last survey, in 2002, in harmony with the 50% reference simulation. Stop-MDA surveys could be conducted to test this prediction.

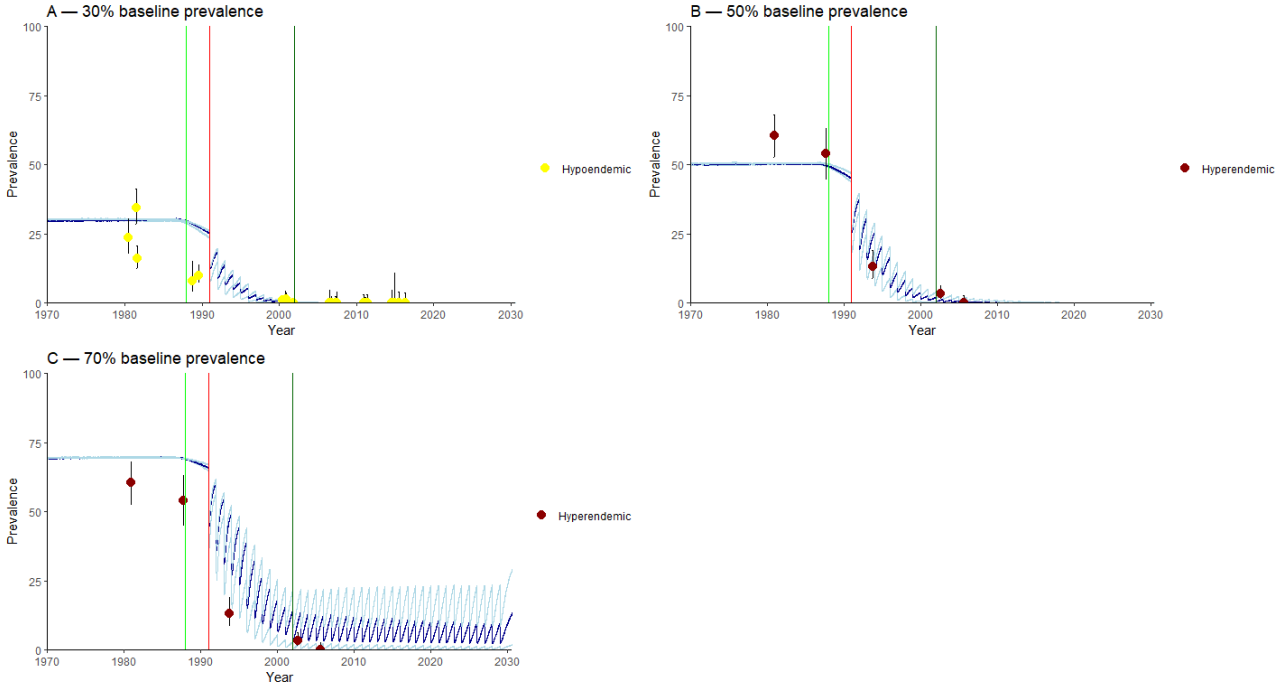


Figure 3.7 — Model outcomes for Maritime with available pre-control endemic prevalence. **(A)** Hypoendemic villages and simulated 30% baseline prevalence; **(B)** Hyperendemic villages and simulated 50% baseline prevalence; **(C)** Hyperendemic villages and simulated 70% baseline prevalence. The village surveys are represented by yellow (hypoendemic) or brown (hyperendemic) dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line). Dark model output coloured lines (blue) indicate simulation results for the reference intervention scenario; light coloured lines (light blue) indicate simulation results for the pessimistic scenario (upper bound) or the optimistic scenario (lower bound).

4. Discussion

4.1 History of Control in Togo and prospects of elimination by 2030

OCP was created with the aim of onchocerciasis EPHP. The program began with weekly aerial application of insecticide to fast-moving waterways where blackflies breed. The original OCP area included only part of Togo, which gradually covered the rest of the nation due to the reinvasion of vectors from the uncontrolled areas. In 1989, ivermectin MDA, the primary control intervention since then, was introduced. OCP ended in 2002, but MoH Togolese has continued to perform MDA by CDTI. Some villages from the northernmost regions were incorporated into the SIZ, with additional MDA and VC until 2007. After the cessation of VC, blackflies populations are expected to gradually recuperate their original pre-OCP levels (Koala *et al.*, 2019; Hougard *et al.*, 2001). There is some uncertainty around the early years of OCP scale-up and implementation, visible in the initial pre-control surveys.

After being the first Sub-Saharan country to EPHP both sleeping sickness and elephantiasis, Togo MoH is looking forward to onchocerciasis EoT. There is the urgency to assess the prospects of EoT by 2030 and define which villages can progress with stop-MDA surveys or implement ATS. For such purposes, mathematical modelling provides valuable understanding of retrospective and prospective trends while accounting for the transmission heterogeneity and density-dependent processes.

The model predictions that agree with the data shows that the prevalence of microfilariae decreased initially slowly with VC and enhanced after the introduction of MDA. Increasing MDA coverage or VC efficacy contribute to the decrease of the prevalence. VC has a limited effect in the highly endemic regions due to the impact on the ABR. For instance, in a holoendemic setting with 60,000 ABR, a VC efficacy of 90% reduces it to 6,000 ABR, a number still related to hyperendemic communities.

The results support the implementation of stop-MDA surveys in the Togolese hypoendemic and mesoendemic villages, as these have less resilience to interventions. According to the simulations that capture the data, most hyperendemic and holoendemic settings will not reach EoT without ATS. However, the combination of VC and ivermectin MDA substantially reduced the prevalence of all villages during the last decade of the OCP, and the reimplementation of VC may provide the extra control required to reach EoT in the highly endemic communities. Control should be markedly

intensified in the SIZ of Kara and Centrale, which involve holoendemic settings. Even during the years of combined interventions, some villages had moderate prevalence, thus being unlikely to reach EoT without substantial ATS.

The analysis of each Togolese region is conveyed in the following paragraphs. Overall, control interventions lowered the prevalence of onchocerciasis, notably in Savanes, Plateaux and Maritime, where the data generally followed optimistic scenarios. Additional control will be needed in some villages, especially those belonging to the SIZ. With appropriate guidance (i.e. following the suggestions provided in the following chapter), Maritime and Savanes are expected to reach EoT before 2030.

4.1.1 Savanes

Villages with a recorded baseline prevalence in Savanes SIZ had remarkable reductions during the first decades of control, almost reaching EoT when SIZ began. Villages without recorded pre-control endemicity had more variable and moderately high prevalence during SIZ. The data and the model for the hyperendemic settings suggest that ATS may be needed to reach EoT in a few highly endemic settings.

Overall, Savanes has more than four decades of interventions against river blindness, and VC appears to have had a notable impact on disease transmission. Onchocerciasis EoT should have been accomplished in hypoendemic, mesoendemic and nearly all hyperendemic villages, and most settings can proceed with stop-MDA surveys in the upcoming years. Some hyperendemic communities and settlements where control have not started until recent year are likely to call for ATS for river blindness EoT, mainly villages part of the SIZ.

4.1.2 Kara

The data suggest that the control interventions had different effects across the region. Kara has villages with all levels of endemicity, up to 95% holoendemicity. The combination of VC and ivermectin MDA was sufficient to reduce the prevalence of all villages, including the most endemic ones. Once the VC stopped, the prevalence increased in several hyperendemic or without documented baseline villages. This highlights the need for ATS in these settings to onchocerciasis EoT.

As a region of high and extremely diverse endemicities, public health officials may not promptly distinguish the most burdened communities. Hence, it may be desirable to implement ATS at the regional level. Further control must be implemented as soon as possible ere the reduction in prevalence due to VC disappears entirely from the highly endemic villages. Stop-MDA surveys may start in hypoendemic, moderately mesoendemic and non-SIZ villages, the latter because the most endemic settings were included in the SIZ.

4.1.3 Centrale

Centrale has a blended record of control interventions, splitting during the OCP between Phase III East and Southern Extension and partially integrating the SIZ. Accordingly, the region has at least two distinct situations, between SIZ and non-SIZ villages. On the one hand, almost all non-SIZ communities are close to or have already reached onchocerciasis EoT and can proceed with stop-MDA surveys. On the other hand, Centrale SIZ has higher prevalence, including holoendemic settings far from eliminating the disease.

Centrale hypoendemic and mesoendemic villages may start the stop-MDA surveys. However, communities of the region part of SIZ are meso- to holoendemic. The data from hyper- and holoendemic villages and the simulations that fit them underline the urge to implement ATS if the region aims to reach EoT by the defined time limit. As multiple villages in Centrale have surveys still with moderate prevalence between 2010 and 2017, ATS at the regional level are strongly endorsed.

4.1.4 Plateaux

In Plateaux, some villages are on the border between hypoendemicity and mesoendemicity or between mesoendemicity and hyperendemicity, fitting into various scenarios. Being a region with moderate endemicities for the disease and having started control later than the northern regions, Plateaux is expected to have low to null prevalence in hypo- to mesoendemic villages. Thus, ivermectin MDA should be extended to the following years, primarily for villages without recorded baseline endemicity that may have started control interventions later. The data and simulations indicate that some hyperendemic villages need to implement ATS.

The EoT target is likely to be met by 2030 in nearly all settings. Still, the region will likely need more time to eliminate river blindness and conduct stop-MDA surveys. In parallel, many of Plateaux's surveys follow the pessimistic scenarios, suggesting that VC and MDA coverage

effectiveness was variable and with limited impact in some communities. This variety is also anticipated since Plateaux is the largest region in Togo and holds the largest rural population.

4.1.5 Maritime

In addition to being the most populous, Maritime is the most urban region in Togo. As such, it is not surprising that it is the least endemic region for onchocerciasis. The bulk of its endemic villages are hypoendemic and mesoendemic and are expected to reach EoT before 2030 with annual ivermectin MDA. Maritime may start stop-MDA surveys at the regional level. There is not enough data on its hyperendemic or holoendemic communities. If they exist and minding the simulations, strong surveillance is advised, and ATS may be implemented.

4.1.6 Onchocerciasis elimination in Togo by 2030 and elimination challenges

In order to reach EoT in 2030, the MDA must end by 2027 so that verification of the interruption of transmission can succeed in the following three years (World Health Organization & African Programme for Onchocerciasis Control, 2010). The EoT is expected to be achieved before the deadline in most Togolese endemic villages, with hypoendemic and mesoendemic areas being advised to proceed with stop-MDA surveys. A selection will be needed to separate hyperendemic communities close to EoT and those in need of ATS.

A subsequent report will compare the output of this thesis with the one from the ONCHOSIM model. The EPIONCHO-IBM simulations should be more pessimistic due to the resistance to control interventions effectiveness provided by the negative density-dependent processes (Hamley *et al.*, 2019). Nonetheless, both models should conclude that some highly endemic settings will not reach EoT until 2030, even with high ivermectin MDA coverage and compliance (Coffeng *et al.*, 2014).

One of the main obstacles to the disease elimination in Togo is how the villages were selected for interventions. The OCP and the SIZ only included villages along rivers with less than 2000 inhabitants, assuming that more urban settings would be less at risk for the disease (Koudou *et al.*, 2018). Hence, it is very likely that not all endemic villages were covered by ivermectin MDA. Since 2016, Togo extended the CDTI to all endemic communities, independently of the population size. Surveillance information of the most populated settlements will provide essential information for predicting when Togo will eliminate the disease.

As for the diagnostic techniques, skin snip microscopy is the golden standard for onchocerciasis, but it is a painful procedure for the patient, relatively insensitive and time-consuming (World Health Organization, 2021). Nodule palpitation can also be applied, but it does not directly measure the microfilarial load of the infected, and it is not specific enough for hypoendemic settings (World Health Organization, 2021). In years to come, new diagnostic methods must be developed and implemented to better monitoring the disease endemicity and define the best interventions for each location (World Health Organization, 2021).

With the regions of Togo progressing towards EoT, surveillance will be vital to monitor and prevent the recrudescence of the parasite. In particular, supervision should be reinforced in areas with high ATPs (i.e. previously hyperendemic and holoendemic foci) or coupled to communities with ongoing transmission. This is extended to the frontiers with the nation three neighbouring countries, none of which have reached EoT yet (O'Hanlon *et al.*, 2016). Special consideration should be taken with the cross-border transmission from Benin and to the South of Savanes (O'Hanlon *et al.*, 2016).

4.2 EPIONCHO-IBM model and onchocerciasis in Togo

The EPIONCHO-IBM model accurately portrays the diverse epidemiological situation in Togo. The model stands out for representing the heterogeneity of blackflies bite exposure by sex and age at the individual level, as well as microfilarial load and compliance to the treatment. Furthermore, EPIONCHO-IBM is stochastic, allowing the random EoT of the parasite in villages with low endemicity. This stochasticity is inverse to the community size and can play a crucial role in EOT for high endemic settings with moderate MDA coverages (Hamley *et al.*, 2019).

EPIONCHO-IBM also considers the negative density-dependent processes that govern the lifecycle of *O. volvulus*. These processes relax with control interventions and enhance the transmission of the parasite and its resilience to control. A final consideration of the weight of the density-dependent processes is the potential spread of parasites with poor responses to ivermectin (Doyle *et al.*, 2017). Territories that recently had ivermectin MDA are at greater risk of developing sub-optimal responders to treatment (Churcher *et al.*, 2009), as it happened in Ghana (Awadzi *et al.*, 2004). This stresses the need to achieve EoT as soon as possible and generate new therapies.

In endemic communities, the worm load is frequently aggregated, with a few individuals harbouring most worms and the bulk of the population burdened by just a few (Anderson, 1985).

This heterogeneity depends on several factors, such as individual blackfly exposure, immune response and genetic variation (Duerr *et al.*, 2003; Filipe *et al.*, 2005; Timmann *et al.*, 2008). EPIONCHO-IBM assumes that non-compliance is independent of individual exposure to blackfly bites, typically true in high coverages and compliances of ivermectin MDA. However, the exposure of non-compliers may be greater than that of compliers, making the EoT challenging and increasing the risk of recrudescence. One might think that the most exposed individuals would have higher microfilarial loads and be more symptomatic and prone to seek treatment. However, dermatological symptoms are not associated with microfilarial load (Kipp & J., 2002), and visual problems are due to past loads rather than current ones (Hopking & Boatin, 2011). Moreover, ivermectin has side effects, especially in individuals with high loads, contributing to non-compliance (Shuford, Turner & Anderson, 2016). Other factors contribute to this behaviour, such as MDA delivery issues, risk of SAE in loiasis co-endemic settings (not the case in Togo), female infertility and hard-to-reach groups (Shuford, Turner & Anderson, 2016; World Health Organization & African Programme for Onchocerciasis Control, 2006). Ultimately, non-compliant individuals may sustain transmission if they have high exposure to *Simulium* bites. Further analyses are required regarding the non-compliance rates to treatment, particularly to the MDAs against filarial parasites.

A final note about non-compliance, it was assumed that this decreases with increasing MDA coverage. If the simulations considered greater non-compliances, the transmission of the disease would be facilitated and the EoT less likely to be achieved (Senyonjo *et al.*, 2016). Thus, it is vital to monitor and ensure high levels of compliance, with future CDTIs making efforts to increase the compliance and address any hard-to-reach groups.

The simulations do not consider local geographical barriers (i.e. mountains) or vector migration, which can be as extensive as 400 kilometres (Basáñez, Churcher & Grillet, 2009). This latter variable is challenging to parameterize since the distance travelled by the vector depends on the *Simulium* species (Basáñez, Churcher & Grillet, 2009). In turn, each endemic setting will have different proportions of each species and data about it could be needed to parametrize the model.

Onchocerciasis can be divided into three *Onchocerca–Simulium* complexes: forest, forest-savannah mosaic and savannah (Cheke & Garms, 2012). The former complex is associated with more L3 infective larvae, while the latter has greater severity (Cheke & Garms, 2012). Although the forest complex is found in Togo (Post *et al.*, 2013), the bulk of the country comprises savannas (83%; Adaptation Fund, 2018). EPIONCHO-IBM is parameterised with information from the savannah complex and is expected to represent Togo epidemiology. Several factors contribute to the different

epidemiological situations between the Togolese regions besides the urbanisation level and type of the *Onchocerca–Simulium* complex. The average temperature is higher in the north (Adaptation Fund, 2018), accelerating the development of the microfilariae into L3 infective larvae in the fly (Cheke *et al.*, 2015). Contrariwise, humidity and precipitation are higher and more variable in Plateaux (Adaptation Fund, 2018), enhancing the development of blackflies larvae. The simuloid population may increase with climate changes (Saker *et al.*, 2004; Otabil *et al.*, 2020) or decrease due to its susceptibility to polluted water (Lock, Adriaens & Goethals, 2014). Conversely, the construction of dams and artificial watercourses as Togo develops may alter the endemicity of nearby villages. It is the case of Abu Hamed, previously the world's northernmost onchocerciasis focus, where the construction of a dam contributed to the EoT (Higazi, 2015). Thus, the dynamics of blackflies and *O. volvulus* larval stages should be regularly monitored to update the endemicity parameterisation.

All the scenarios modelled simulated annual CDTI. However, some villages have received ivermectin biannually during SIZ (Yaméogo, 2008; World Health Organization & African Programme for Onchocerciasis Control, 2006), and, since 2016, 15 Togolese districts have implemented biannual CDTI (END in Africa, 2016). Considering this intervention in the simulations was not feasible since there is still no information available at a district or region level. This contribution to reducing onchocerciasis prevalence may be counterbalanced by more modest coverages of recent MDAs[3] (Gebrezgabiher *et al.*, 2019), also not accounted for in the simulations.

Overall, EPIONCHO-IBM can be a vital tool to inform onchocerciasis control and elimination policies and understand transmission dynamics. The model provides key insights on the feasibility of EoT according to the interventions in place and the history of control.

4.3 Alternative Treatment Strategies (ATS)

Several ATS are being considered against river blindness. Perhaps the most straightforward to implement is ivermectin MDA biannually or pluriannually (Boussinesq, Fobi & Kuesel, 2018; Coffeng *et al.*, 2014). Similarly, MDA with more effective drugs, such as moxidectin (Milton *et al.*, 2020), or a combination of drugs can reduce the time to EoT (Boussinesq, Fobi & Kuesel, 2018).

[3] The primary determinant for the decrease in therapeutic coverage MDA was that Togo started to consider all endemic areas for the disease beyond 2000 inhabitants. Such obstacle was overcome after a couple of years (World Health Organization, 2018, 2020b, 2019; Gebrezgabiher *et al.*, 2019).

One of the most promising ATS is anti-*Wolbachia* therapies to eliminate the endosymbiont *Wolbachia pipiens* (i.e. antibiotic doxycycline, Hoerauf et al., 2008). The bacterium is crucial for the larval development, fertility and survival of *O. volvulus*. Another option can be to complement MDA with VC (Boussinesq, Fobi & Kuesel, 2018). Although larviciding is not a viable long-term ATS due to its high cost, it can be introduced during the peak of seasonal transmission. There are additional VC strategies under consideration, such as "Esperanza Window Trap" (to decrease the biting rate around villages, Loum et al., 2019), and "Slash and Clear" (to remove vegetation from blackflies breeding sites and reduce larval support, Jacob et al., 2018).

Lastly, CDTI delivery has the potential to be maximised. Being given by the populations, they are the ones that decide when to distribute the MDA. Ideally, ivermectin should be offered when vectors are more abundant to reduce microfilarial loads and the number of infected flies, especially in regions with high baseline endemicities (Turner *et al.*, 2015).

4.4 Concluding remarks

Before control interventions, Togo was one of the most endemic countries for river blindness in the world (World Health Organization & African Programme for Onchocerciasis Control, 2010). The EPIONCHO-IBM model fairly represented the varied epidemiological situations regionally and across time. There is still some uncertainty around the biological parameters of O. volvulus. Further investigation should be conducted to better understand the density-dependent processes and parasite fecundity (i.e. worm fecundity over its age and treatment).

One of the most outstanding achievements of the onchocerciasis interventions in Togo is the MDA therapeutic coverage, which was regularly above the required target during both the former EPHP and current EoT targets. However, challenges still reside to include all areas of difficult access and hard-to-reach individuals, migratory populations and potential to optimise the CDTI.

The feasibility of EoT by ivermectin MDA is shown to be strongly dependent on the level of initial endemicity. Most Togolese hypoendemic and mesoendemic villages can progress to stop-MDA surveys. ATS will be vital to support the most endemic settings. In the coming years, as the country reaches EoT, surveillance will be critical in areas at risk of recrudescence, such as those with high biting rates or coupled with endemic zones.

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Appendix I

Most villages in Togo started ivermectin MDA between 1988 and 1993 (Table I). Some parts of Savanes and Maritime began later as they had an effective VC or low endemicity levels.

Table I — Year of MDA start for each region and SIZ status of Togo.

Region		Year of MDA start % of villages (% villages with baseline)					
		1988	1991	1992	1993	1995	2000
Savanes	Non-SIZ		16.7%		33.3% (100%)		50.0%
	SIZ	4.7% (25.0%)			90.7% (75.0%)		4.6%
Kara	Non-SIZ	63.6%		9.1%	9.1%	18.2% (100.0%)	
	SIZ	73.4% (81.8%)		2.5% (9.1%)		24.1% (9.1%)	
Centrale	Non-SIZ		100.0% (100.0%)				
	SIZ	20.0% (100.0%)	80.0%				
Plateuax			62.9% (64.4%)	27.8% (27.4%)	9.3% (8.2%)		
Maritime			9.3% (16.7%)		90.7% (83.3%)		
Nationwide		16.6% (7.4%)	43.9% (63.1%)	10.7% (14.1%)	22.6% (14.1%)	5.0% (1.3%)	1.2%

Appendix II

Villages lacking information on baseline endemicity

The EPIONCHO-IBM model outputs at the region and SIZ status levels are described below for the villages without information on baseline endemicity. In this case, all endemic prevalence scenarios were plotted together with the data in order to compare observations with predicted microfilarial temporal dynamics. The model simulations that best capture the data are presented in dark blue.

II.1 Savanes non-SIZ

The villages lacking baseline prevalence information seem to be best reflected by mesoendemic simulations and may reach EoT with annual ivermectin MDA before 2030 (Fig. II.1). Assuming that these villages had similar control interventions as those with baseline data, they would also follow the reference and pessimistic intervention scenarios for Savanes non-SIZ (Fig. II.1B, C). The 50% reference scenario is the one that best matches the data and supports the trend to reach EoT with by 2020 (Fig. II.1B).

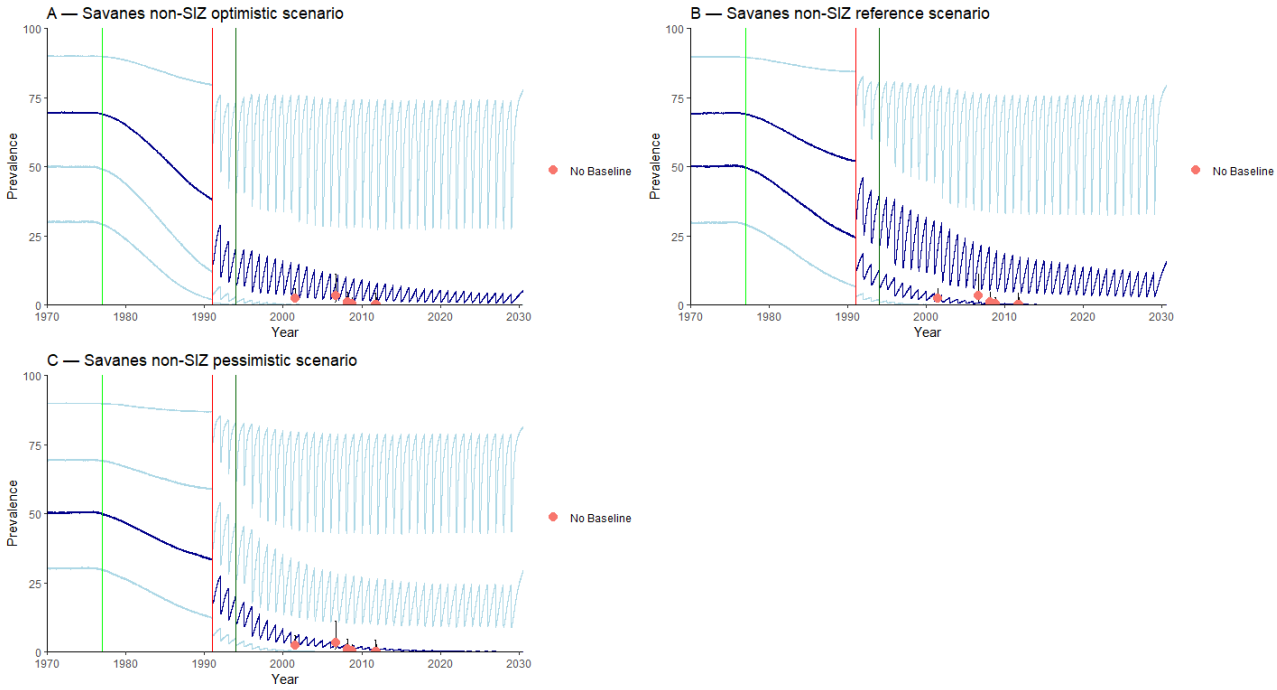

Figure II.1 — Model outcomes for Savanes non-SIZ lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. **(A)** Optimistic, **(B)** Reference, **(C)** Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).

II.2 Savanes SIZ

If the villages without recorded baseline endemicity had similar control interventions as those with baseline data, they would follow the optimistic scenario for Savanes SIZ (Fig. II.2A. B). Accordingly, the bulk of villages withou rol prevalence information may have l - to hyperendemic. Some follow the 50% optimistic scenario (Fig. II.2A), reaching null prevalence before 2002. However, most settings fit the 50% pessimistic model (Fig. II.2C), with very low to null prevalence between 2010 and 2017. One village distinctly follows the 70% reference simulation, and its prevalence has stabilised since 1990 (95% CIs between 0.1 and 5.4% Microfilarial prevalence). Another community only has a survey in 2014 with a prevalence of 9.0% (95% CI from 2.5 to 27.8%). ATS are required in the) villages and may be helpful to accelerate EoT in some settings.

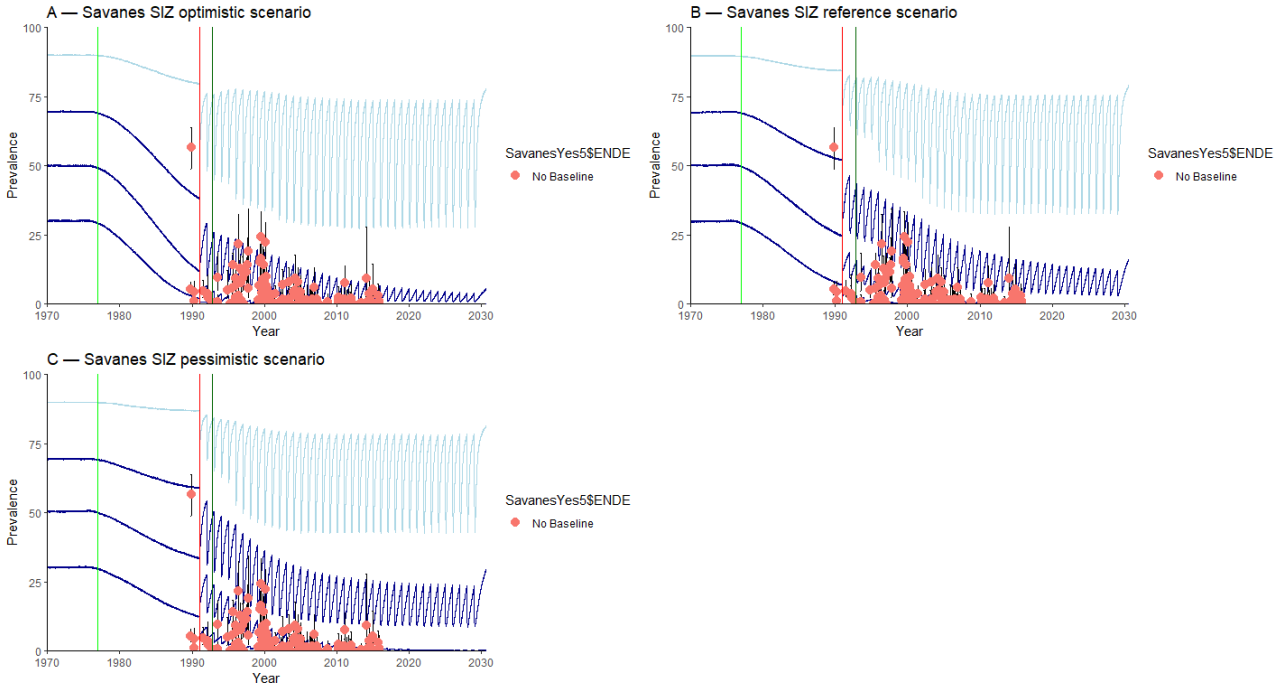

Figure II.2 — Model outcomes for Savanes SIZ lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. **(A)** Optimistic, **(B)** Reference, **(C)** Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).

II.3 Kara non-SIZ

The villages in Kara that lack baseline information seem to follow the 50% endemic prevalence scenario with reference intervention scenario (Fig. II.3B) or the 50% endemic prevalence scenario, without any positive prevalence of the disease after 2011. Additional interventions may be necessary to reach EoT in one of the villages, which has had a stable prevalence of three to five per cent since 2002 (95% CIs from 2.5% to 7.5%), following 70% endemic prevalence with reference intervention scenario (Fig. II.3B).

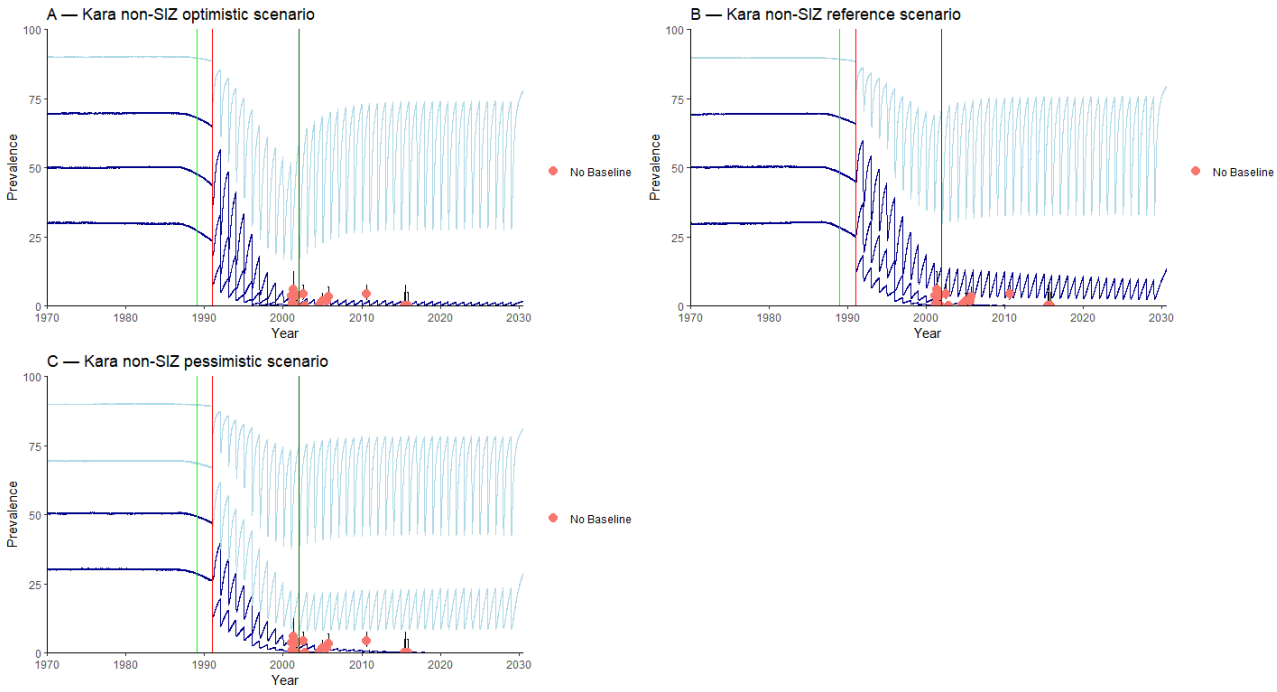

Figure II.3 — Model outcomes for Kara non-SIZ lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. (A) Optimistic, (B) Reference, (C) Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).

II.4 Kara SIZ

The data seem to be captured within the range of baseline endemicities and intervention scenarios simulated (Fig. II.4). The prevalence appears to decrease in every community during the period of combination of VC and ivermectin MDA, only to rise sharply following the cessation of VC. This is an area of concern, where intensified ATS will be needed in putative hyperendemic and holoendemic villages to reach EoT.

Ultimately, some communities only have one survey, not enough to define a trend or know if they start interventions later than the rest of the region.

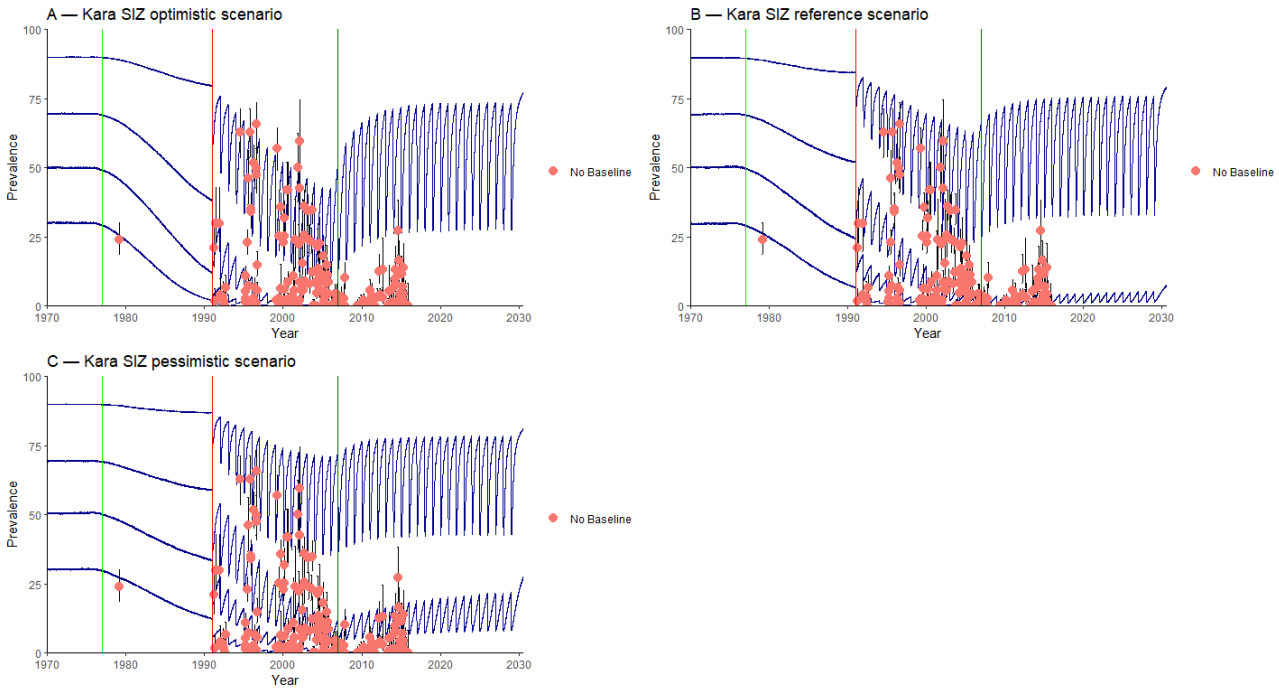

Figure II.4 — Model outcomes for Kara SIZ lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. (A) Optimistic, (B) Reference, (C) Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).

II.5 Centrale non-SIZ

Most of the infection trends for these villages, without data on baseline endemicity, seem to be compatible with pre-control mesoendemic levels of transmission (Fig. II.5), and broadly consistent with the 50% endemic prevalence with reference (having null by the last survey, Fig. II.5B) or pessimistic (almost reaching zero prevalence, Fig. II.5C) intervention scenarios. In a couple of communities, the reduction in prevalence appears to have reached a plateau since the end of VC, fitting the 70% endemic prevalence with optimistic intervention (Fig. II.5A) scenario. This latter predicted infection trend suggests ongoing transmission.

The Takade village only has one survey available, in 2015, with 14.5% microfilarial prevalence (95% CI from 10.7% to 19.2%). ATS should be implemented promptly for this community.

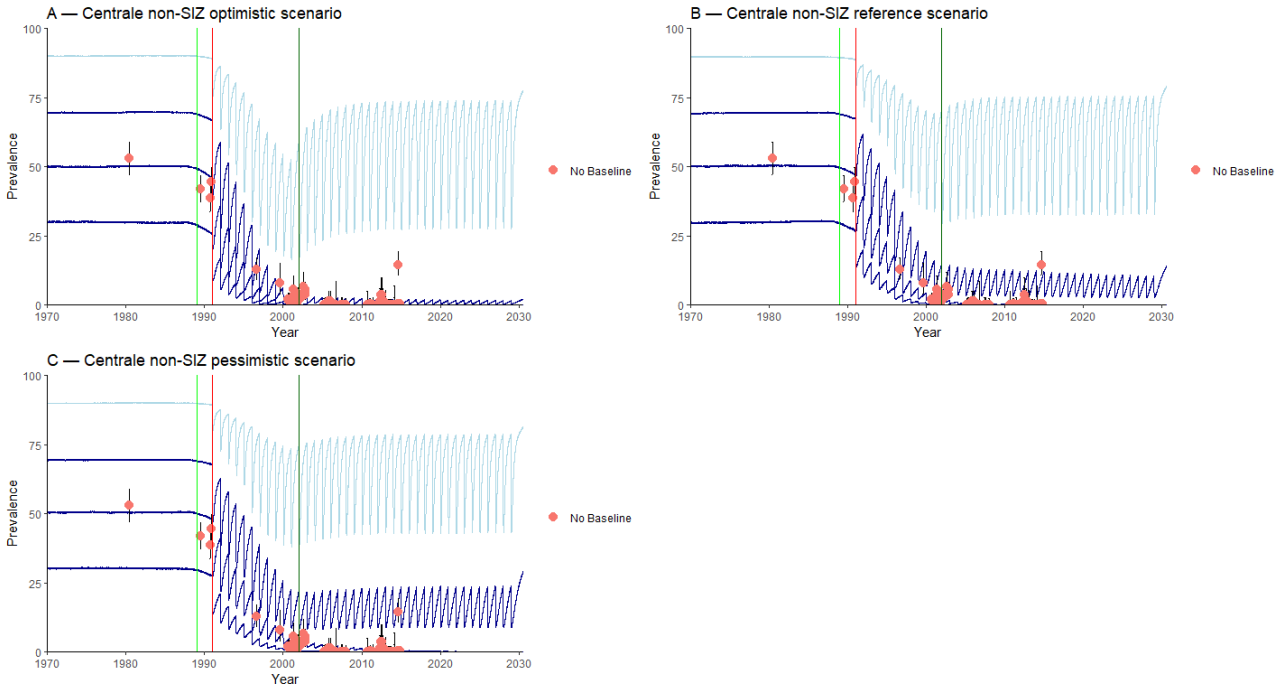

Figure II.5 — Model outcomes for Centrale non-SIZ lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. **(A)** Optimistic, **(B)** Reference, **(C)** Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).

II.6 Centrale SIZ

Most of the infection trends in these villages seem to be compatible with pre-control meso- to holoendemic levels of transmission (Fig. II.6), particularly the 50% endemic prevalence with optimistic intervention scenario (Fig. II.6A), 70% prevalence with reference or pessimistic interventions simulations (Fig. II.6B, C) and 90% prevalence with optimistic intervention scenario (Fig. II.6A). This also is an area of concern, as annual ivermectin MDA as the sole intervention does not appear to be sufficient to reach EoT.

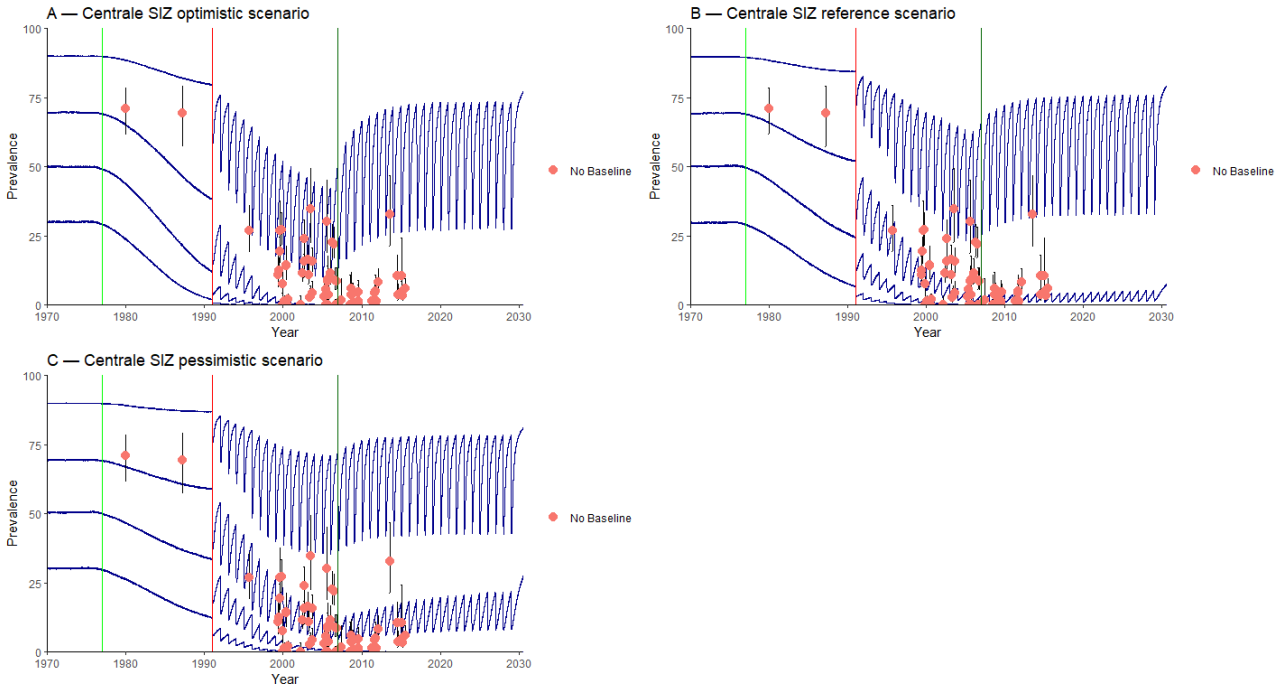

Figure II.6 — Model outcomes for Centrale SIZ lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. **(A)** Optimistic, **(B)** Reference, **(C)** Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).

II.7 Plateaux

Similar to the baseline endemicity villages, Plateaux non-baseline communities have varying prevalence (Fig. II.7). Hypoendemic and mesoendemic villages appear to be reaching EoT by 2020, following the 30% and 50% scenarios. Several mesoendemic and low hyperendemic communities need ivermectin MDA for a couple of years more. Hyperendemic settings require ATS to decrease prevalence, which has increased or stabilised since VC ended.

Plateaux has two surveys before the overall start of VC in the region. They belong to the Djodji village, where VC started in 1976 to eliminate the Djodji form of *Simulium* flies.

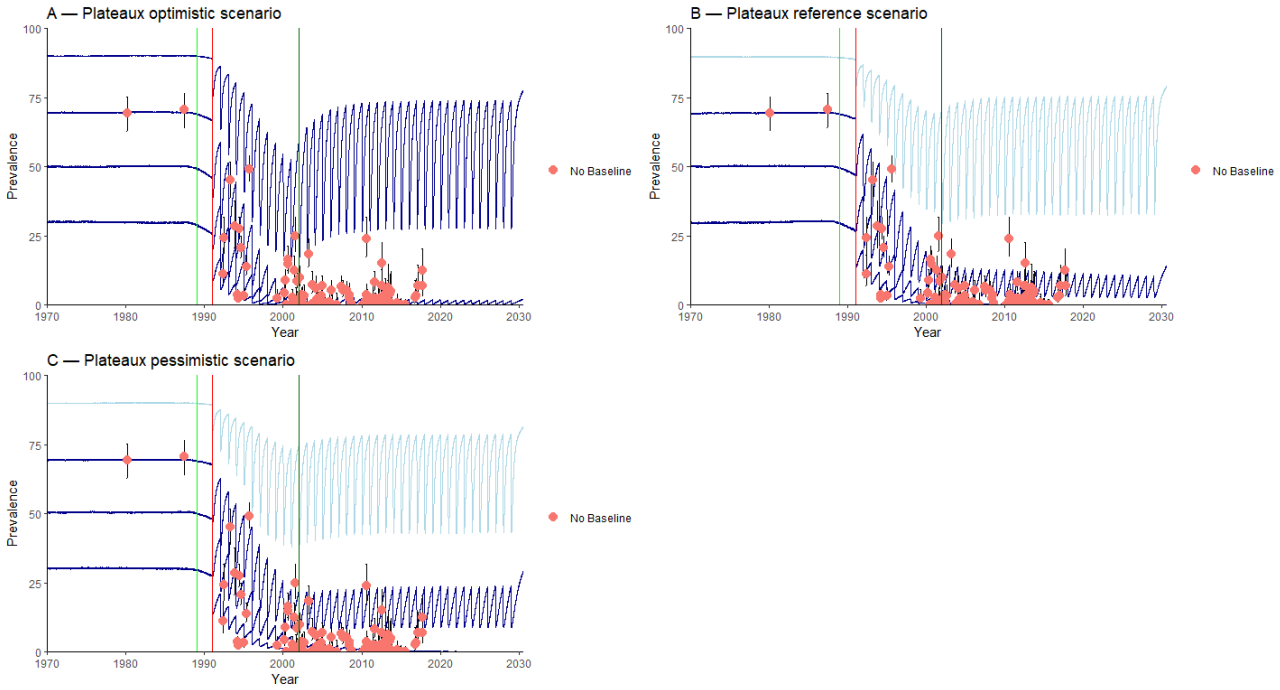

Figure II.7 — Model outcomes for Plateaux lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. **(A)** Optimistic, **(B)** Reference, **(C)** Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).

II.8 Maritime

As with baseline villages, Maritime surveys without pre-control endemicity are of low prevalence (Fig. II.8). All settlements follow the 30% and 50% baseline endemicity scenarios and should reach EoT by 2030. There is no apparent data from hyperendemic settings.

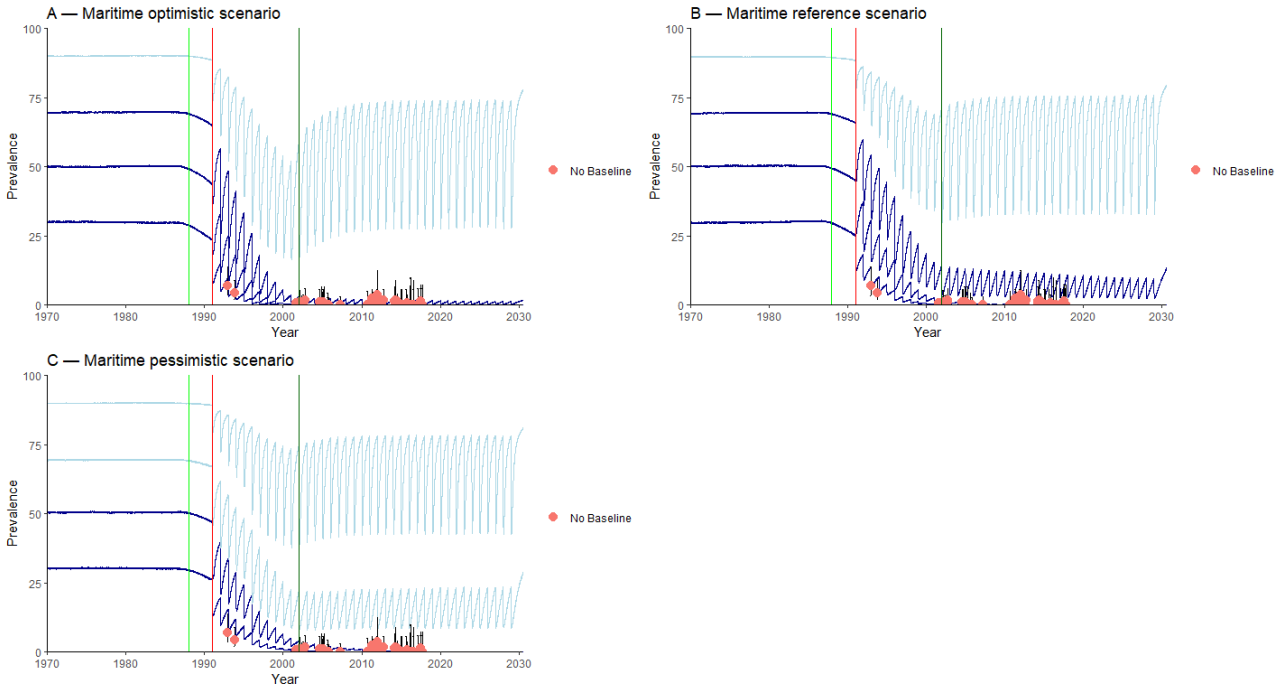

Figure II.8 — Model outcomes for Maritime lacking information on pre-control endemic prevalence. For each intervention scenario, all four endemic prevalence scenarios (30%, 50%, 70% and 90%) are presented. **(A)** Optimistic, **(B)** Reference, **(C)** Pessimistic intervention scenarios. The village surveys are represented by pink dots with 95% Wilson CIs. Vertical lines denote start of VC (light green line); end of VC (dark green line), and start of ivermectin MDA (red line).