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Modelling the elimination of river blindness using long-term epidemiological and programmatic data from Mali and Senegal

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ABSTRACT

The onchocerciasis transmission models EPIONCHO and ONCHOSIM have been independently developed and used to explore the feasibility of eliminating onchocerciasis from Africa with mass (annual or biannual) distribution of ivermectin within the timeframes proposed by the World Health Organization (WHO) and endorsed by the 2012 London Declaration on Neglected Tropical Diseases (i.e. by 2020/2025). Based on the findings of our previous model comparison, we implemented technical refinements and tested the projections of EPIONCHO and ONCHOSIM against long-term epidemiological data from two West African transmission foci in Mali and Senegal where the observed prevalence of infection was brought to zero circa 2007–2009 after 15–17 years of mass ivermectin treatment. We simulated these interventions using programmatic information on the frequency and coverage of mass treatments and trained the model projections using longitudinal parasitological data from 27 communities, evaluating the projected outcome of elimination (local parasite extinction) or resurgence. We found that EPIONCHO and ONCHOSIM captured adequately the epidemiological trends during mass treatment but that resurgence, while never predicted by ONCHOSIM, was predicted by EPIONCHO in some communities with the highest (inferred) vector biting rates and associated pre-intervention endemicities. Resurgence can be extremely protracted such that low (microfilarial) prevalence between 1% and 5% can be maintained for 3–5 years before manifesting more prominently. We highlight that post-treatment and post-elimination surveillance protocols must be implemented for long enough and with high enough sensitivity to detect possible residual latent infections potentially indicative of resurgence. We also discuss uncertainty and differences between EPIONCHO and ONCHOSIM projections, the potential importance of vector control in high-transmission settings as a complementary intervention strategy, and the short remaining timeline for African countries to be ready to stop treatment safely and begin surveillance in order to meet the impending 2020/2025 elimination targets.

Abbreviations: ABR, annual biting rate; APOC, African Programme for Onchocerciasis Control; CDTI, community-directed treatment with ivermectin; MAP, maximum a posteriori; MDA, mass drug administration; mf, microfilariae; NTD, neglected tropical disease; OCP, Onchocerciasis Control Programme in West Africa; PES, post-elimination surveillance; PTS, post-treatment surveillance; SIR, sampling importance resampling; WHO, World Health Organization.

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1. Introduction

Human onchocerciasis or river blindness is caused by the filarial nematode *Onchocerca volvulus* and is earmarked for elimination by the World Health Organization (WHO) as articulated by the 2012 Roadmap (WHO, 2012) and the London Declaration on Neglected Tropical Diseases (2012). The principal strategy to achieve elimination is mass drug administration (MDA) with ivermectin. Ivermectin kills the skin-dwelling microfilariae (mf) that are the progeny of adult *O. volvulus* and are infectious to biting blackfly species vectors. Ivermectin may also kill and/or sterilize adult worms (Gardon et al., 2002). Multiple rounds of mass treatment are effective in lowering the prevalence and intensity of onchocerciasis and – if given for long enough at high enough coverage – can lead to the interruption of transmission and elimination of the infection. In Latin America, (biannual) MDA has successfully eliminated onchocerciasis from Colombia (West et al., 2012), Ecuador (Lovato et al., 2014), northern Venezuela (Convit et al., 2013) and Mexico (Rodríguez-Pérez et al., 2015), with Guatemala awaiting certification. Good progress towards elimination has also been made in Africa (Tekle et al., 2016) which bears 99% of the onchocerciasis burden, with notable successes in regions of Mali, Senegal (Diawara et al., 2009; Traore et al., 2012), Nigeria (Tekle et al., 2012), Sudan (Higazi et al., 2013) and eastern Uganda (Katabarwa et al., 2014) but also conspicuous regions of ongoing transmission despite years of intervention in Ghana (Lamberton et al., 2015), Cameroon (Katabarwa et al., 2013a; Wanji et al., 2015; Eisenbarth et al., 2016) and northwestern Uganda (Katabarwa et al., 2013b), and evidence of recrudescence in Burkina Faso (Koala et al., 2017).

EPIONCHO and ONCHOSIM are mathematical transmission models of human onchocerciasis that have been used to evaluate the effectiveness of different intervention strategies in reaching the 2020/2025 elimination targets for onchocerciasis (WHO, 2012; APOC, 2012). Both models have been used to predict the time to eliminate onchocerciasis under annual or biannual MDA (Coffeng et al., 2014a; Turner et al., 2014), and have been used in collaboration with the African Programme for Onchocerciais Control (APOC) to evaluate how progress towards elimination can be accelerated by implementing alternative treatment strategies (WHO, 2015). ONCHOSIM has been used to inform the Onchocerciasis Control Programme in West Africa (OCP) and the African Programme for Onchocerciasis Control on expected trends of infection during vector control (Plaisier et al., 1991), mass ivermectin treatment (Winnen et al., 2002; Coffeng et al., 2014a; Tekle et al., 2016) or their combination (Plaisier et al., 1997), the health impact of the interventions (Coffeng et al., 2014b), and the expected time to elimination (Kim et al., 2015).

More recently, the developers of EPIONCHO and ONCHOSIM have started to compare and refine their models, with the objective of reaching consensus on the feasibility of and time horizons for elimination, and optimum interventions for achieving the WHO goals in Africa (Stolk et al., 2015). The first formal comparison, which attempted to 'dock' the two models by making parameter assumptions as equivalent as possible, revealed some important differences between the models' structural assumptions and resulting outputs. Both models demonstrated a benefit of biannual versus annual treatment but differed in their predicted time to elimination, particularly when using transmission breakpoints as endpoints rather than operational (microfilarial) prevalence thresholds such as those provisionally proposed by APOC (2010). One of the conclusions of this first comparison was that the use of a single prevalence threshold across different endemicity (transmission intensity) settings may not be appropriate and needs further investigation (Stolk et al., 2015).

The epidemiology of onchocerciasis has changed as a result of the introduction of ivermectin MDA, which means that EPIONCHO and ONCHOSIM are now being used in transmission contexts far from those in which they were originally developed and parameterized (Basáñez and Boussinesq, 1999; Plaisier et al., 1991; Plaisier et al., 1995). Hence, to maintain confidence in projections, these models must be tested and validated against data collected before, during and after MDA, reflecting the spectrum of transmission conditions, from endemic infection to transmission interruption and elimination (Basáñez et al., 2012a,b). Given the prolonged nature of onchocerciasis interventions, capturing and recording such data is challenging and resource-intensive and would probably have been impossible without the logistical and technical support of the OCP and APOC.

Here we test the EPIONCHO and ONCHOSIM models against epidemiological data collected over two decades from 27 sentinel communities in two onchocerciasis foci in Mali and Senegal. In these foci, MDA with ivermectin alone has successfully brought the prevalence of infective larvae (in blackflies) and of mf (in humans) – detectable by skin snips – to zero, indicative of elimination (Diawara et al., 2009; Traore et al., 2012). In particular, prevalence of skin mf reached the previously proposed operational thresholds set by APOC of <5% in all surveyed villages and <1% in 90% of those surveyed (APOC, 2010). We use programmatic data on the frequency and coverage of MDA with ivermectin to simulate these interventions from endemic baseline, circa 1987, through to cessation of treatment, circa 2006, and then beyond, projecting forwards to 2020. We train the model projections using subsets of epidemiological data comprising community-specific estimates of microfilarial prevalence collected throughout the intervention. We determine whether the models predict sustained elimination or resurgence of infection in the post-treatment and post-elimination periods (WHO, 2016) and explore how these predictions change when using increasing amounts of epidemiological training data, from pre-intervention data only to multiple longitudinal data points per community.

2. Models and methods

2.1. EPIONCHO

EPIONCHO is a deterministic onchocerciasis transmission model that uses partial differential equations to describe changes (with respect to time and host age) in mean number of fertile and non-fertile female adult worms per host, mean number of mf per milligram (mg) of skin in humans and mean number of larvae per simuliid (blackfly) vector. Briefly, the model is based on a prototype presented by Basáñez and Boussinesq (1999), and extended to include age and sex structure of the human population (Filipe et al., 2005); the temporal dynamics of mf following ivermectin treatment (Basáñez et al., 2008), and increased programmatic realism related to patterns of treatment coverage and systematic non-adherence (Turner et al., 2013). The model allows for age- and sex-specific patterns of exposure to blackfly bites (Filipe et al., 2005) and variation in adherence to treatment. The latter is modelled by partitioning the population into four groups, namely, a full adherence group that takes treatment every round; two semi-adherent groups that take treatment every other round alternately, and a systematically non-adherent group that never takes treatment. Treatment with ivermectin is assumed to kill 98–99% mf, temporarily sterilize adult female worms and cumulatively reduce their capacity to produce mf (Basáñez et al., 2008; Turner et al., 2013). EPIONCHO has been used to address public health policy questions including an economic evaluation of implementing community-directed treatment with ivermectin (CDTI) biannually