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Supporting Information

S1. Seasonality of transmission

EpiOncho was modified to permit the instantaneous biting rate (the number of bites received per person per unit time) of blackfly vectors to vary within the year to reflect seasonality in the transmission of onchocerciasis. It is assumed that in the absence of vector control operations, the entomological conditions during the treatment programme remain unchanged. A sinusoidal functional form recently used to model seasonality in malaria transmission [1] was parameterized to reflect two scenarios of seasonal transmission (Figure S1 and Table S1) typical in Africa:

Seasonal transmission scenario 1: An extreme scenario with transmission occurring during a rainy season typically lasting between four to five months each year; based on the entomological situation in foci of Senegal, Mali [2, 3] and Nigeria [4], where elimination has been reported.

Seasonal transmission scenario 2: A longer period of transmission, still peaking in the rainy season but not ceasing completely in the dry season; motivated by the entomological observations conducted in Nigeria and reported in [5].

Figure S1: Investigated scenarios of seasonal transmission, illustrated for a pre-control endemicity of 40% microfilarial prevalence. The red and blue lines correspond to, respectively, seasonal transmission scenario 1 and seasonal transmission scenario 2 (see text above). The area under the curve (i.e. the average instantaneous biting rate over the year) corresponds to the annual biting rate or ABR (17,038 bites/person/yr for scenario 1 and 9,148 bites/person/yr for scenario 2 – the difference in the ABR’s is due to the (negative) density dependent processes governing the establishment of incoming worms within the human host [6, 7]). The parameter definitions and values are presented in Table S1.
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### Supplementary Table S1. Parameter definitions and values describing seasonality in onchocerciasis transmission

| Symbol | Definition of variables and parameters | Expression, average value and units | Ref. |
|--------|--------------------------------------|-------------------------------------|------|
| $BR(t)$ | Instantaneous biting rate at time $t$ | $X^c \left[ c + (1-c) \left\{ 1 + \cos[2\pi(t-u)] \right\} \right]^\kappa$ | [1] |
| $X$ | The peak instantaneous biting rate | 40% pre-control mf prevalence  
Scenario 1: 69,281  
Scenario 2: 24,019  
60% pre-control mf prevalence  
Scenario 1: 223,438  
Scenario 2: 56,688  
80% pre-control mf prevalence  
Scenario 1: 489,531  
Scenario 2: 231,281 | This work |
| $c$ | Determines the minimum instantaneous biting rate ($=c^\cdot X$, with $0 \leq c \leq 1$) | Scenario 1: 0  
Scenario 2: 0.112 | This work |
| $u$ | The position of the transmission peak in relation to treatment timing | Scenario 1: Varied  
Scenario 2: Varied | This work |
| $\kappa$ | Shape parameter describing the biting pattern (for $\kappa > 0$) | Scenario 1: 4.9  
Scenario 2: 3.2 | This work |
| $ABR$ | Annual biting rate, no. of bites/person/year | $ABR = \int_{t=0}^{t=1} BR(t) dt$, for $u = 0$ | This work |
| $\beta$ | Biting rate per fly on humans assuming a human blood index of 0.3 and biting every 3.5 days | 31.25 yr$^{-1}$ | [7, 8] |
| $m(t)$ | Vector to host ratio at time $t$ | $BR(t) / \beta$ | |

Scenarios are described in section S.1. Seasonality of transmission. mf prevalence: microfilarial prevalence.
S.2. Estimating the dynamic effects on skin microfilarial loads induced by treatment with moxidectin

The following differential equations and illustration (Figure S2) describe the rate of change with respect to time of the mean number of non-fertile (N) and fertile (F) adult female worms per person, and the mean number of microfilariae per mg of skin (M), parameters defined in Supporting Table S.2.

\[
\frac{dN}{dt} = \Delta + (\beta_0 + \beta_1(\tau))F - \left(a_0 + \mu_0^W\right)N
\]

\[
\frac{dF}{dt} = a_0N - (\beta_0 + \beta_1(\tau) + \mu_0^W)F
\]

\[
\frac{dM}{dt} = \varepsilon F - \left(\mu_0^M + \mu_1^M(\tau)\right)M
\]

**Figure S2:** Schematic representation of the model and the corresponding differential equations. The parameter definitions and values are presented in Table S2.

The model is identical to that used in a previous meta-analysis to estimate the dynamic effects of ivermectin on microfilarial loads [9]. Here, \( \mu_0^W(\tau) \) (the capita death rate of microfilariae following treatment) and \( \beta_1(\tau) \) (the treatment-induced per capita rate at which fertile females become non-fertile) were re-estimated by fitting the model to phase II moxidectin clinical trial data [10] on the percentage reduction from pre-treatment in mean microfilarial load at different times after treatment with 8 mg moxidectin (8 days; 1, 2, 3, 6, 12 and 18 months, Figure 1). Both of these rates depend on the time since treatment, \( \tau \). It was assumed that a single 8 mg dose of moxidectin has no macrofilaricidal effect (i.e. does not kill the adult worms, i.e. the macrofilariae). The model was fitted to the data by (nonlinear) least-squares regression, following the approach taken in [9], yielding parameter estimates presented in Table S2.
### Supplementary Table S2. Definitions and values of parameters and variables determining microfilarial load dynamics following treatment with moxidectin

| Symbol | Definition of variables and parameters | Expression, average value and units | Ref. |
|--------|----------------------------------------|-------------------------------------|------|
| $\Delta$ | Rate at which incoming, initially non-reproducing, female worms establish within onchocercal nodules (i.e. the force of infection) | Arbitrary value, $yr^{-1}$ | |
| $\mu_{0}^a$ | Per capita death rate of adult worms | $0.1 \ yr^{-1}$ | [6] |
| $\alpha_0$ | Per capita rate at which untreated non-reproducing female worms become fertile | $0.59 \ yr^{-1}$ | [9] |
| $\beta_0$ | Per capita rate at which untreated fertile female worms become naturally non-fertile | $0.33 \ yr^{-1}$ | [9] |
| $\varepsilon$ | Rate of production of microfilariae per fertile female worm scaled by the total weight (in milligrams) of microfilariae-bearing skin | $1.1538 \ yr^{-1}$ | [6, 11] |
| $\mu_{0}^{u}$ | Per capita death rate of microfilariae in the absence of treatment | $0.8 \ yr^{-1}$ | [6] |
| $\tau$ | Time since last treatment | years | – |
| $\beta_{1}(\tau)$ | Excess per capita rate at which fertile female worms become non-fertile following treatment (embryostatic effect) | $\beta_{1} = \beta_{1}^{\max} \ exp(-\gamma \ \tau) \ yr^{-1}$ | [9] |
| $\beta_{1}^{\max}$ | The maximum per capita rate of treatment-induced sterility | Moxidectin: 462 $yr^{-1}$ (*), Ivermectin: 32.4 $yr^{-1}$ | This work |
| $\gamma$ | The rate of decay of treatment-induced sterility with time after treatment | Moxidectin: 4.83 $yr^{-1}$ (*), Ivermectin: 19.6 $yr^{-1}$ | This work |
| $\mu^{\prime\prime}_{1}(\tau)$ | Excess per capita death rate of microfilariae following treatment (microfilaricidal effect) | $\mu^{\prime\prime}_{1} = (\tau + \nu)^{-\sigma} \ yr^{-1}$ | [9] |
| $\nu$ | Constant added to time after treatment to allow for a very large, yet finite, microfilaricidal effect at the point of treatment | Moxidectin: 0.04 (*), Ivermectin: 0.0096 | This work |
| $\sigma$ | Shape parameter for the per capita death rate of microfilariae following treatment | Moxidectin: 1.82 (*), Ivermictin: 1.25 | This work |

*The values indicated with an asterisk were estimated in this work as described in the legend of Figure S2.
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Supplementary Table S3: Summary of pre-control epidemiology (perennial transmission), African savannah

| Pre-control endemicity level | Microfilarial prevalence | Annual biting rate $^\text{§}$ | Annual transmission potential $^\text{¶}$ | Mean intensity $^*$ (mf per mg) | Mean intensity $^*$ in those aged ≥ 20 (mf per mg) |
|-----------------------------|--------------------------|-------------------------------|-------------------------------------|-----------------------------|----------------------------------|
| Mesoendemic                 | 40%                      | 7,305                         | 88                                  | 11.2                        | 18.7                             |
| Hyperendemic                | 60%                      | 15,472                        | 373                                 | 23.9                        | 40.0                             |
| Highly hyperendemic         | 80%                      | 85,800                        | 4,290                               | 58.9                        | 98.0                             |

$^\text{§}$ Annual biting rate (ABR): the average number of *Simulium damnosum* s.s./ *S. sirbanum* bites to which a person is exposed during a whole year.

$^\text{¶}$ Annual transmission potential (ATP): the average number of infective larvae (L3) of *Onchocerca volvulus* potentially received during a whole year by a person exposed to the annual biting rate.

$^*$ Both the ABR and ATP are for a proportion of vector blood meals of human origin equal to 0.3 [6].

$^*$ Arithmetic mean microfilarial load per mg of skin; note that this is different to the community microfilarial load (CMFL), which is the geometric mean microfilarial load per skin snip in those aged 20 years and above) [12].
Supplementary Table S4: Sensitivity to the magnitude of the assumed anti-macrofilarial action of ivermectin and moxidectin of the additional programme duration and cost of switching from annual community-directed treatment with ivermectin (aCDTI) to biannual CDTI (bCDTI) or annual community directed treatment with moxidectin (aCDTM)

| Schedule of ivermectin treatment strategy and initial level of onchocerciasis endemicity | 1% cumulative reduction in microfilarial production by female adult worms per dose | 7% cumulative reduction in microfilarial production by female adult worms per dose | 30% cumulative reduction in microfilarial production by female adult worms per dose |
|---|---|---|---|
| | Projected duration, in years, of treatment programme (relative cost, in percent) | Projected duration, in years, of treatment programme (relative cost, in percent) | Projected duration, in years, of treatment programme (relative cost, in percent) |
| | aCDTI | bCDTI (†) | aCDTM(‡,†) | aCDTI | bCDTI(†) | aCDTM(‡,†) | aCDTI | bCDTI(†) | aCDTM(‡,†) |
| 30% microfilarial prevalence | | | | | | | | |
| Mesoendemic | 20 | 13(115%) | 11(63%,55%) | 16 | 10(109%) | 10(68%,62%) | 11 | 8(122%) | 9(84%,69%) |
| Hyperendemic | 32 | 19(113%) | 17(65%,58%) | 24 | 16(119%) | 16(74%,62%) | 16 | 14(144%) | 14(90%,63%) |
| Highly hyperendemic | NA | 24(66%,53%) | NA | 22(63%,65%) | NA | 19(109%) | 20(71%,65%) | | |
| 20% microfilarial prevalence | | | | | | | | |
| Mesoendemic | 20 | 13(115%) | 11(63%,55%) | 16 | 10(109%) | 10(68%,62%) | 11 | 8(122%) | 9(84%,69%) |
| Hyperendemic | 29 | 17(110%) | 15(63%,57%) | 21 | 13(111%) | 13(69%,62%) | 15 | 13(143%) | 13(89%,63%) |
| Highly hyperendemic | NA | 20(58%,52%) | NA | 19(76%,64%) | 32 | 18(109%) | 19(71%,65%) | | |
| 15% microfilarial prevalence | | | | | | | | |
| Mesoendemic | 20 | 13(115%) | 11(63%,55%) | 16 | 10(109%) | 10(68%,62%) | 11 | 8(122%) | 9(84%,69%) |
| Hyperendemic | 25 | 14(104%) | 12(58%,56%) | 19 | 11(104%) | 12(70%,67%) | 13 | 11(139%) | 12(94%,68%) |
| Highly hyperendemic | NA | 22(100%) | 17(52%,52%) | NA | 15(75%) | 17(52%,69%) | 30 | 17(108%) | 18(71%,66%) |

† Percentage cost relative to aCDTI. ‡ Percentage cost relative to bCDTI. NA: Operational thresholds for treatment interruption not attained within the 50-year time horizon (and percentage of costs calculated based on costs of 50 years of treatment). CDTM: community-directed treatment moxidectin, CDTI: community-directed treatment with ivermectin. This analysis was performed with a 50-year time horizon, discount rate of 3% applied to the costs, therapeutic coverage of 80%, 0.1% of systematic non-compliers, perennial transmission and pOTTIS <1.4% microfilarial prevalence. Costs do not include the value of the (donated) drugs.
Supplementary Table S5: In-country costs to reach provisional operational threshold for treatment interruption followed by surveillance (pOTTIS) of annual community-directed treatment with moxidectin (aCDTM) relative to community-directed treatment with ivermectin (CDTI) for two assumptions on the cost of implementing aCDTM.

| Schedule of treatment strategy and initial level of onchocerciasis endemicity | Cost (per year) of aCDTM relative to aCDTI |
|---|---|
| Annual moxidectin treatment implemented from start of the programme | Same | 10% higher |
| Mesoendemic | 71%, 63% | 78%, 69% |
| Hyperendemic | 76%, 65% | 84%, 72% |
| Highly hyperendemic | 70%, 63% | 77%, 69% |

| Switching to moxidectin treatment at different levels of microfilarial prevalence during an ongoing annual treatment programme | Additional total costs* of aCDTM relative to continuing aCDTI, and switching to bCDTI |
|---|---|
| 30% microfilarial prevalence | Mesoendemic | 68%, 60% | 75%, 66% |
| Hyperendemic | 74%, 62% | 81%, 68% |
| Highly hyperendemic | 63%, 65% | 69%, 71% |
| 20% microfilarial prevalence | Mesoendemic | 68%, 62% | 75%, 69% |
| Hyperendemic | 69%, 62% | 76%, 68% |
| Highly hyperendemic | 56%, 64% | 62%, 71% |
| 15% microfilarial prevalence | Mesoendemic | 68%, 62% | 75%, 69% |
| Hyperendemic | 70%, 67% | 77%, 74% |
| Highly hyperendemic | 52%, 69% | 57%, 76% |

aCDTM: annual community-directed treatment moxidectin

* The ratio of additional costs is considered from the point of switching from annual to biannual treatment (as opposed to from the start of control). When switching from annual to biannual treatment, infection (microfilarial) prevalence was assumed to be measured just before the next round of treatment distribution. The analysis was performed with a 50-year time horizon, discount rate of 3% applied to the costs, therapeutic coverage of 80%, 0.1% of systematic non-compliers, perennial transmission, and 7% cumulative reduction in microfilarial production by female adult worms per treatment dose. pOTTIS < 1.4% microfilarial prevalence. Costs do not include the value of the (donated) drugs.
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**Supplementary Table S6: Sensitivity to the assumed discount rate of the relative total programme cost of annual community-directed treatment with moxidectin (aCDTM) compared to annual or biannual community-directed treatment with ivermectin (aCDTI, bCDTI)**

| Treatment strategy and initial level of onchocerciasis endemicity | Total costs of aCDTM in % of costs of aCDTI, and bCDTI | Discount rate |
|------------------------------------------------------------------|--------------------------------------------------------|---------------|
| aCDTM implemented from start of the programme                    |                                                        |               |
| Mesoendemic                                                      | 65%, 63%                                               | 71%, 63%      | 76%, 62%      |
| Hyperendemic                                                     | 68%, 66%                                               | 76%, 66%      | 83%, 65%      |
| Highly hyperendemic                                              | 52%, 63%                                               | 70%, 63%      | 84%, 63%      |

| Switching to aCDTM at different levels of microfilarial prevalence in an ongoing annual CDTI programme | Additional total costs* of aCDTM relative to continuing aCDTI, and switching to bCDTI |               |
|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------|
| 30% microfilarial prevalence                                                                       | Mesoendemic                                                                       | 63%, 61%      | 68%, 60%      | 74%, 61%      |
|                                                                                                     | Hyperendemic                                                                       | 67%, 63%      | 74%, 62%      | 81%, 62%      |
|                                                                                                     | Highly hyperendemic                                                                | 44%, 66%      | 63%, 65%      | 78%, 64%      |
| 20% microfilarial prevalence                                                                       | Mesoendemic                                                                       | 63%, 63%      | 68%, 62%      | 74%, 63%      |
|                                                                                                     | Hyperendemic                                                                       | 62%, 63%      | 69%, 62%      | 76%, 62%      |
|                                                                                                     | Highly hyperendemic                                                                | 38%, 66%      | 56%, 64%      | 73%, 65%      |
| 15% microfilarial prevalence                                                                       | Mesoendemic                                                                       | 63%, 63%      | 68%, 62%      | 74%, 63%      |
|                                                                                                     | Hyperendemic                                                                       | 63%, 68%      | 70%, 67%      | 76%, 67%      |
|                                                                                                     | Highly hyperendemic                                                                | 34%, 71%      | 52%, 69%      | 68%, 67%      |

aCDTM: annual community-directed treatment moxidectin, aCDTI: annual community-directed treatment with ivermectin, bCDTI: biannual community-directed treatment with ivermectin. * The ratio of additional costs is considered from the point of switching from annual to biannual treatment (as opposed to from the start of control). Modelling assumptions are as in the legend of Table S5.
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