Feasibility of onchocerciasis elimination using a "test-and-not-treat" strategy in *Loa loa* co-endemic areas

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Summary: Our model predicts that onchocerciasis can be eliminated using test-and-not-treat (TaNT) in *L. loa* co-endemic areas. The required treatment duration using TaNT would be only slightly longer than in areas with conventional MDA, provided that participation is good.

Abstract

Background

Mass drug administration (MDA) with ivermectin is the main strategy for onchocerciasis elimination. Ivermectin is generally safe but associated with serious adverse events in individuals with high *Loa loa* microfilarial densities (MFD). Therefore, ivermectin MDA is not recommended in areas where onchocerciasis is hypo-endemic and *L. loa* is co-endemic. To eliminate onchocerciasis in those areas, a test-and-not-treat (TaNT) strategy has been proposed. We investigated whether onchocerciasis elimination can be achieved using TaNT and the required duration.

Methods

We used the individual-based model ONCHOSIM to predict the impact of TaNT on onchocerciasis microfilarial (mf) prevalence. We simulated pre-control mf prevalence levels from 2-40%. The impact of TaNT was simulated under varying levels of participation, systematic non-participation and exclusion from ivermectin due to high *L. loa* MFD. For each scenario, we assessed the time to elimination, defined as bringing onchocerciasis mf prevalence below 1.4%.

Results

In areas with 30-40% pre-control mf prevalence, the model predicted that it would take between 14 and 16 years to bring the mf prevalence below 1.4% using conventional MDA, assuming 65% participation. TaNT would increase the time to elimination by up to 1.5 years, depending on the level of systematic non-participation and the exclusion rate. At lower exclusion rates (≤2.5%), the delay would be less than six months.

Conclusions

Our model predicts that onchocerciasis can be eliminated using TaNT in *L. loa* co-endemic areas. The required treatment duration using TaNT would be only slightly longer than in areas with conventional MDA, provided that participation is good.

Keywords: Onchocerciasis; *Loa loa*; point-of-care testing; elimination; modelling

Background

Mass drug administration (MDA) with ivermectin is the main strategy for the elimination of onchocerciasis. Although ivermectin is generally safe, the drug has been associated with serious adverse events (SAE) in persons with *Loa loa*,[1] a filarial parasite endemic in forest areas of Central Africa.[2] People with *L. loa* microfilarial densities (MFD) greater than 30,000 microfilariae per milliliter (mf/mL) of blood are at high risk of developing potentially fatal encephalopathy.[3, 4] Since the 1990s, more than 500 SAE cases with encephalopathy have been reported after treatment with ivermectin, of which 60 led to death.[4, 5]

The World Health Organization (WHO)/Mectizan Donation Program guidelines approve ivermectin MDA in meso- and hyperendemic onchocerciasis areas (i.e. onchocercal nodule prevalence >20% in adults) with loiasis co-endemicity, if accompanied by enhanced surveillance for adverse events.[6] The potential benefits of MDA (e.g. prevention of blindness and onchodermatitis) were felt to outweigh the potential risk of *Loa*-related post-ivermectin SAEs and early supportive care of SAE cases could reduce the risk of mortality and long-term sequelae. However, there is no WHO-endorsed strategy for hypoendemic onchocerciasis areas with loiasis co-endemicity, which hinders onchocerciasis elimination.

In order to eliminate onchocerciasis in those areas, a "test-and-not-treat" (TaNT) strategy has been proposed.[5] In a pilot study in Cameroon, the LoaScope (a mobile video microscope scope [7]) was used to rapidly identify individuals with a loiasis MFD of ≥ 20,000 mf/mL, who were then excluded from subsequent ivermectin treatment.[5] In this study, the risk threshold was lowered for safety reasons. The participation rate in health areas varied between 51.5% and 68.4% of the total population, which was considered acceptable given the history of post-ivermectin loiasis-related SAEs in 1999 (after which ivermectin distribution was interrupted in hypoendemic onchocerciasis areas). Overall, only 2.1% of the subjects tested with the LoaScope were excluded from ivermectin treatment due to high loiasis MFD. During the second TaNT campaign in 2017, this percentage dropped to 1.5%. Of the individuals treated with ivermectin in the first round, 99.97% remained below the risk threshold, indicating that those individuals could have been safely retreated without retesting.[8]

While the TaNT strategy has been successfully piloted in Cameroon, it remains unclear whether elimination of onchocerciasis is possible using this strategy and how long the program would have to be continued. We address these questions by mathematical modelling. For this purpose, we used the individual-based model ONCHOSIM[9, 10], which has been used previously to predict the impact of mass treatment on infection trends and to estimate the required treatment duration for achieving elimination.[10-12]

Methods

Model

ONCHOSIM is a stochastic individual-based model that simulates the transmission of onchocerciasis in a closed dynamic population of approximately 440 individuals (rural village).[13, 14] The model simulates life histories of human individuals and *Onchocerca volvulus* worms and mf within individual human hosts. Transmission of infection occurs through bites of blackflies whose intensity is represented by the annual biting rate. The probability that an individual is bitten by a blackfly is assumed to depend on age (exposure to blackfly increases linearly between the ages of zero and 20), sex (higher exposure in males), personal factors (e.g. attractiveness to blackflies), and seasonal biting variation of blackflies. At each bite, blackflies can transmit or pick up the infection. Only a small proportion of transmitted larvae will successfully develop into adult worms. Following insemination of females by male worms, mf are produced, which can be picked up by the blackfly. These mf develop in the blackfly into the infective stage (L3), which is modelled deterministically in the vector. Infection acquired from other villages is captured by the parameter called external force of infection. Our model did not account for an association between onchocerciasis and loiasis intensity within individuals, as evidence suggests that the association is weak and insufficient to explain very high loiasis MFD.[15] Table S1 provides information about the quantification of biological parameters.

Pre-control setting

We simulated hypoendemic pre-control *O. volvulus* mf prevalence between 2-40%, by varying setting-specific transmission parameters: the annual biting rate, the shape of the gamma distribution describing variation in exposure between individuals, and the level of external force of infection. Parameter values were sampled from a predefined parameter space, and were accepted when the resulting pre-control mf prevalence in the endemic equilibrium would fall into one of the bins: 2-5%, 5-10%, 10-15%, 15-20%, 20-25%, 25-30%, 30-35%, 35-40%. The model was run until we had 1,000 parameter combinations for each bin. The sampled parameter space and the underlying distribution of the intensity of infection are provided in Figure S1 and S2.

Treatment scenarios

Test-and-not-treat strategy

The modelled TaNT strategy includes annual testing with the LoaScope of individuals for high loiasis MFD, which is repeated during the entire period of the simulation. Individuals who tested negative, i.e. loiasis MFD <20,000 mf/mL, were provided ivermectin. In our model, treatment with ivermectin was assumed to kill 99% of *O. volvulus* mf within one month.[16]

The probability of participation of individuals in TaNT rounds is determined by age, sex and a lifelong participation factor. Children under the age of five years and a proportion of women in the reproductive age (pregnant or lactating) are excluded from TaNT, because they are not eligible to receive ivermectin. The lifelong participation factor (score between 0 and 1) represents personal circumstances that makes an individual less (low score) or more likely (higher score) to participate.[9, 10] Some individuals may never participate, because they are chronically ill or refuse treatment, and are represented by the proportion of systematic non-participation.

The participation rate is defined as the percentage of the total population that is tested per round. With lower participation rates, systematic non-participation would be more likely. To cover realistic scenarios, we defined seven participation scenarios varying both the participation rate (50%, 65% and 80%) and the systematic non-participation (0%, 5%, and 10%) (Table S2).

As a result of TaNT, an additional percentage of the individuals tested is excluded from ivermectin because of high loiasis MFD. On average 2.1% of those tested was excluded from ivermectin during the pilot TaNT campaign.[5] To capture possible heterogeneity across endemic areas, we varied the exclusion rate: 1%, 2.5%, 5%, 7.5% and 10%. Since loiasis MFD in individuals has been found to be stable over time, we assume that individuals with high loiasis MFD remain excluded from ivermectin during their whole lifetime.[17] TaNT exclusion is modeled similarly to systematic non-participation.

In the main analysis, we assumed that the annual TaNT exclusion rate remains fixed. However, observations from the second TaNT round in Okola showed that the exclusion dropped from 2.1% to 1.5% within 18-months.[8] In a sensitivity analysis, we explored the impact of a decreasing exclusion rate. To match the observed change, we assumed an exponential drop (rate: 0.22 per year) in the first 10 TaNT rounds and no exclusion due to high loiasis MFD in the following rounds.

Mass drug administration

As a reference scenario, we explored the impact of conventional ivermectin MDA (i.e. without pre-testing), in which no one was excluded from treatment because of loiasis. Ivermectin MDA is simulated by specifying the time and coverage of the treatment. In order to compare this scenario head-to-head with the TaNT scenarios, we simulated annual ivermectin MDA using the same participation rates and systematic non-participation as in the TaNT scenarios.

Analysis

For pre-control mf prevalence levels between 2-40%, we predicted the impact of TaNT in loiasis co-endemic areas and the impact of annual ivermectin MDA (reference scenario) over a period of 25 years.

In our scenarios, we assume that treatment in the main village and neighboring villages are started simultaneously, resulting in a drop of the external force of infection over time. To estimate the decline in the external force of infection, we simulated a hyperendemic area with annual ivermectin MDA and used the modeled rate of decline in the force of infection as a proxy (Figure S3).

For each treatment scenario, we assessed the time until elimination of onchocerciasis. As in previous studies, we defined elimination as reaching a modelled mf prevalence below 1.4% (i.e. operational threshold for treatment interruption followed by surveillance).[9, 18] We ran the model for 50 years and assessed the year in which the mf prevalence first fell below 1.4% per run. If the target was not met, we assumed a duration until elimination of 50 years (equals the simulated period). Per treatment scenario, we then calculated the mean required treatment duration per pre-control level. We only present the results over a period of 25 years.

For each treatment scenario, we also assessed the annual probability of achieving elimination, which was calculated as the proportion of runs in which the mf prevalence fell below 1.4% per year by pre-control setting.

Our study follows to the modelling principles of the NTD Modelling Consortium for policy-relevant work (Table S3).[19]

Results

Figure 1 shows the trend in onchocerciasis mf prevalence of the upper end of the hypoendemic profile (30-40%), assuming 65% participation with 5% systematic non-participation. Using conventional ivermectin MDA, elimination of onchocerciasis could be achieved after an average of 15 years. Implementing the TaNT strategy, assuming 5 and 10% TaNT exclusion, prolongs the mean time until elimination by 0.7 and 1.4 years, respectively.

The delay in achieving onchocerciasis elimination using a TaNT strategy compared to conventional ivermectin MDA depends on the pre-control onchocerciasis mf prevalence, participation rate, systematic non-participation, and TaNT exclusion (Figure 2). Areas with lower levels of pre-control mf prevalence, higher participation rates and lower proportions of systematic non-participation would reach elimination sooner compared to areas with higher prevalence, lower participation and higher systematic non-participation. Areas with a pre-control mf level above 25% would not reach elimination within 25 years if the participation rate were 50%. Elimination could be reached within 25 and 15 years if 65% and 80% of the population participates, respectively.

Table 1 summarizes the average time to elimination for all treatment scenarios. Higher pre-control mf levels increase the time to onchocerciasis elimination by 2 to 5-fold compared to 2-10% pre-control mf prevalence. A 65% and 50% participation would increase the time to elimination by 1.4-fold and >2-fold compared to 80% participation, respectively. The time to elimination increases with higher TaNT exclusion rates. This increase is larger for areas with high pre-control onchocerciasis mf prevalence levels and high levels of systematic non-participation. At an exclusion of 10%, the time to elimination increases by 1.7, 1.5 and 3 years at most, assuming a 80%, 65%, and 50% participation, respectively. At lower levels of TaNT exclusion (i.e. $\leq$2.5%), the delay to reach the assumed elimination threshold compared to ivermectin MDA varies between 0.0-0.4, 0.0-0.3 and 0.1-0.8 years, assuming a 80%, 65%, and 50% participation, respectively.

The probability of achieving onchocerciasis elimination increases with TaNT rounds in areas with 30-40% pre-control mf prevalence (Figure 3). Reaching elimination within 25 years is very likely if the participation is 80% or 65%, and very unlikely if the participation is 50%. Lower rates of systematic non-participation and TaNT exclusion would increase the probability of reaching the elimination threshold.

When we assume that the TaNT exclusion rate decreases over time, the time to elimination would be 0.6 and 1.3 years shorter (assuming an initial exclusion rate of 5% and 10%, respectively) compared to a fixed exclusion rate (Figure 4).

Discussion

This study suggests that onchocerciasis can be eliminated in *L. loa* co-endemic areas using a TaNT strategy provided that participation is good. In areas with 30-40% pre-control mf prevalence, it would normally take approximately 14 to 16 years to bring onchocerciasis mf prevalence below 1.4% using conventional ivermectin MDA assuming 65% participation. A TaNT strategy would increase the duration of reaching elimination by only 1.5 years if 10% of the population were excluded from ivermectin treatment. At lower exclusion rates (≤2.5%) the delay would be less than six months, which is very promising. The most challenging areas will be those that are in the upper end of the hypoendemic profile. In these areas, the delay is generally longer and therefore more TaNT rounds and a higher participation would be required.

Our results support the notion that good participation with minimal systematic non-participation are essential to eliminate onchocerciasis.[11] This holds true for both conventional ivermectin MDA and TaNT. A 65% participation rate of the total population may be considered acceptable but increasing it to 80% would further shorten the duration of elimination programs, especially in areas with pre-control onchocerciasis mf prevalences of ≥20%. If participation were as low as 50%, it is very unlikely that onchocerciasis would be eliminated within 25 years, especially if a large proportion of the population is systematically not treated (due to systematic non-particpation or TaNT exclusion). Reaching high participation for TaNT might be more difficult than for ivermectin MDA, because blood samples need to be taken during daytime hours due to the diurnal periodicity of *L. loa* mf in the peripheral blood, making TaNT less flexible logistically.[20] In the pilot TaNT campaign, the participation varied between 51.5% and 68.4% of the total population.[5] Low participation was believed to be the result of fear of SAEs based on past experiences with neurological SAEs and deaths. In the second round, participation was higher and varied between 60.5% and 78% of the total population.[8] Another TaNT campaign conducted in 2017-2018 in the neighboring Soa health district and involving local health personnel and community volunteers showed an overall participation of approximately 66% in rural settings.[21] Urban and semi-urban areas show consistently lower rates of participation.[5, 21] The rationale of getting tested for safe treatment might lead to higher willingness to participate in future rounds, which could further reduce the time until elimination. Involvement of local personnel and volunteers might add trust and participation. Also, health education strategies have been suggested to increase participation.[22]

To reach the assumed elimination threshold, our main findings suggest that TaNT should be repeated for 14.5 to 17.4 years in areas with pre-control onchocerciasis mf levels 30-40% and 65% participation. In Okola (pre-control mf prevalence: 15.3-29.9%),[5] the time to elimination would range between 11.3 and 14.6 years assuming 65% participation and 2.5% exclusion. Although sustaining TaNT for a long period would create a burden on health care systems in terms of operational challenges and costs, it is encouraging that the present study predicts that TaNT would delay elimination by a maximum of only 1.5 years. Moreover, it is very likely that the proportion that needs to be excluded due to high loiasis MFD will decrease over time. If an optimistic decreasing rate of exclusion is assumed, this could reduce the time to elimination by up to 1.3 years (Figure 4). In order to reduce the operational challenges and cost of TaNT, testing only those who were not tested previously or were excluded due to high loiasis MFD should be considered. After several years, the number of individuals requiring testing would be small. Conventional MDA could be organized for individuals who have taken ivermectin before, and TaNT at the health area or district level for those

requiring testing. Such an approach would further reduce the time to elimination and costs. Generally, the number of people who (after participating in TaNT) take ivermectin is crucial for onchocerciasis elimination.

Alternative treatment strategies might be considered particularly in areas with higher pre-control onchocerciasis mf levels, because those areas would require more effort on the part of programs to ensure good participation rates and minimal systematic non-participation. Mass treatment with a drug that is effective for onchocerciasis and safe to use in people with high loiasis MFD would be programmatically preferred. For example, drugs that work by killing the *Wolbachia* symbiont of *O. volvulus* worms (not present in *L. loa* worms) or other macrofilaricidal only or both micro- and macrofilaricidal drugs could be considered. An example is doxycycline, which is known to have macrofilaricidal activity against *O. volvulus* but does not affect *L. loa*.[23, 24] Unfortunately, doxycycline is impractical to use on a large scale, because of the long regimen (4-6 weeks) and contra-indications in pregnant women and children under 12 years of age. Alternatively, a macrofilaricide could be provided only to individuals excluded from ivermectin due TaNT, and after testing for *O. volvulus*. Such an approach would lower the transmission intensity and would likely decrease the required time to elimination of onchocerciasis. This would only be practical if the percentage of exclusion were low. In order to further reduce the time to elimination, complementary vector control might be considered as an additional measure.[25]

As in previous studies, we defined elimination as reaching a modelled mf prevalence below 1.4%. Whether the chosen threshold would lead to elimination of transmission strongly depends on pre-control mf levels and local transmission conditions.[26] At lower transmission intensities, a low threshold may not be necessary to achieve elimination. In fact, elimination of transmission, defined as 99% probability of elimination 50 years post-treatment, could be achieved after 5 to 6 years of treatment in hypoendemic settings, meaning that elimination could already be achieved at a higher mf prevalence threshold than the suggested 1.4% (Figure S4). This threshold also depends on the assumed level exposure heterogeneity. When a lower level of exposure heterogeneity is assumed, elimination could be achieved sooner. The 1.4% threshold used in this study can be regarded as conservative, and it is very likely that elimination of transmission would be achieved when this threshold is reached.

In reality, the infection dynamics will be influenced by movement of infected humans or flies, as well as changes in demographic, geographic, and environmental conditions. To account for movement of infected humans or flies, our model includes an external force of infection representing incoming infections from neighboring areas. The level of control in neighboring areas is an important determinant for the success and duration of elimination programs in a certain village. If treatment (e.g. ivermectin MDA) in neighboring areas occurred earlier, time to elimination would drop by 4 to 6 years (Figure S5). Moreover, if we assume no incoming infections from neighboring villages, elimination could be achieved without intervention in some situations.

Conclusions

Our model predicts that onchocerciasis can be eliminated using TaNT in hypoendemic areas co-endemic for *L. loa*. Assuming good participation, the required duration of TaNT to reach a threshold of 1.4% mf prevalence would be only slightly longer than in areas with conventional ivermectin MDA. It will be most challenging to achieve elimination in areas that are in the upper end of the hypoendemic profile. In such areas, elimination could take more than 15 years depending on participation and TaNT exclusion rates.

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Author Contributions

DB, JK, SP, HN-D, YN-E, CC, CM, AK, DF, TN, SdV, MB, and WS contributed to the planning of the study, interpretation of the results, and reporting of the work. DB and WS conducted the analysis. All authors have read and approved the manuscript.

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Potential Conflict of Interest

DF has a patent for High Numerical Aperture Telemicroscopy Apparatus (US Patents 8 743 194 and 8 786 695), licensed to Thermo Fisher Scientific. All other authors declare no competing interests.

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Tables

Table 1. Average time needed to reach an onchocerciasis mf prevalence below 1.4% by pre-control mf prevalence level

Systematic non-participation	Strategy	TaNT exclusion	Time to onchocerciasis mf prevalence <1.4% [a]											
			80% participation				65% participation				50% participation			
			Pre-control				Pre-control				Pre-control			
			2-10%	10-20%	20-30%	30-40%	2-10%	10-20%	20-30%	30-40%	2-10%	10-20%	20-30%	30-40%
None	MDA[b]	None	3.6	7.5	9.1	10.0	4.9	10.5	13.0	14.3	7.1	17.8	>25.0	>25.0
	TaNT[c]	1.0%	3.6	7.7	9.2	10.2	4.9	10.6	13.1	14.5	7.2	18.0	>25.0	>25.0
		2.5%	3.7	7.8	9.4	10.5	5.0	10.7	13.3	14.6	7.2	18.1	>25.0	>25.0
		5.0%	3.9	8.1	9.8	10.9	5.2	11.0	13.6	15.0	7.4	18.4	>25.0	>25.0
		7.5%	4.0	8.4	10.2	11.4	5.4	11.2	13.9	15.3	7.6	18.8	>25.0	>25.0
		10.0%	4.2	8.7	10.6	11.7	5.5	11.4	14.2	15.6	7.7	19.3	>25.0	>25.0
5%	MDA[b]	None					4.9	10.7	13.5	15.0	7.1	18.5	>25.0	>25.0
	TaNT[c]	1.0%					5.0	10.8	13.6	15.1	7.2	18.6	>25.0	>25.0
		2.5%					5.1	11.0	13.8	15.3	7.3	18.7	>25.0	>25.0
		5.0%					5.3	11.3	14.1	15.7	7.5	19.3	>25.0	>25.0
		7.5%					5.4	11.5	14.4	16.0	7.6	19.6	>25.0	>25.0
		10.0%					5.5	11.7	14.8	16.4	7.8	19.9	>25.0	>25.0
10%	MDA[b]	None					5.0	11.0	14.2	15.9	7.2	19.1	>25.0	>25.0
	TaNT[c]	1.0%					5.1	11.2	14.3	16.0	7.3	19.2	>25.0	>25.0
		2.5%					5.2	11.4	14.5	16.3	7.4	19.5	>25.0	>25.0
		5.0%					5.3	11.6	14.9	16.6	7.5	19.9	>25.0	>25.0
		7.5%					5.4	11.8	15.2	17.1	7.7	20.0	>25.0	>25.0
		10.0%					5.6	12.1	15.6	17.4	7.8	20.7	>25.0	>25.0

[a] Mean duration to reach the elimination threshold per pre-control bin; The colors indicate the duration: gradient from green (short duration) to red (long duration); [b] Ivermectin mass drug administration without pre-testing, i.e. no exclusion; [c] Test-and-not-treat strategy

Figures

Figure 1. Trends of onchocerciasis mf prevalence in a setting with 30-40% pre-control mf prevalence assuming 65% participation with 5% systematic non-participation. The mf prevalence was calculated every year before the start of a test-and-not-treat (TaNT) round. Any changes within a year are not shown. Panel A presents the results of individuals runs, showing the variation between those runs. Panel B shows the mean mf prevalence for all runs. The black line represents the reference scenarios, i.e. ivermectin MDA without pre-testing. The red and blue lines represent the TaNT strategy assuming 5 and 10% exclusion due to high *L. loa* MFD, respectively. We assume that TaNT is continued during the entire simulation period. The dashed line depicts the elimination threshold of 1.4% mf prevalence.

Figure 2. Average time needed to reach an onchocerciasis mf prevalence below 1.4% by pre-control level. The black line represents the reference scenarios, i.e. ivermectin MDA without pre-testing. The red and blue lines represent TaNT assuming 5 and 10% exclusion due to high *L. loa* MFD, respectively. Each panel shows results under varying assumptions of participation (i.e. 80%, 65%, and 50%) and systematic non-participation (i.e. 0%, 5%, and 10%).

Figure 3. Probability of reaching an onchocerciasis mf prevalence below 1.4% in a setting with 30-40% pre-control mf prevalence. The black line represents the reference scenarios, i.e. ivermectin MDA without pre-testing. The red and blue lines represent TaNT assuming 5 and 10% exclusion due to high *L. loa* MFD, respectively. Each panel shows results under varying assumptions of participation (i.e. 80%, 65%, and 50%) and systematic non-participation (i.e. 0%, 5%, and 10%).

Figure 4. Trend of onchocerciasis mf prevalence in a setting with 30-40% pre-control mf prevalence assuming a fixed versus a decreasing annual exclusion percentage. The solid line represents the scenario assuming a fixed annual exclusion rate due to high *L. loa* MFD during all treatment rounds. The dotted line represents the scenario assuming an exponentially drop in the annual exclusion with a rate of 0.22 per year in the first 10 years, followed by no exclusion afterwards. The red and blue colored lines represent TaNT assuming an initial exclusion rate of 5 and 10% due to high *L. loa* MFD, respectively. The horizontal dashed line is the onchocerciasis elimination threshold.

Figure 1

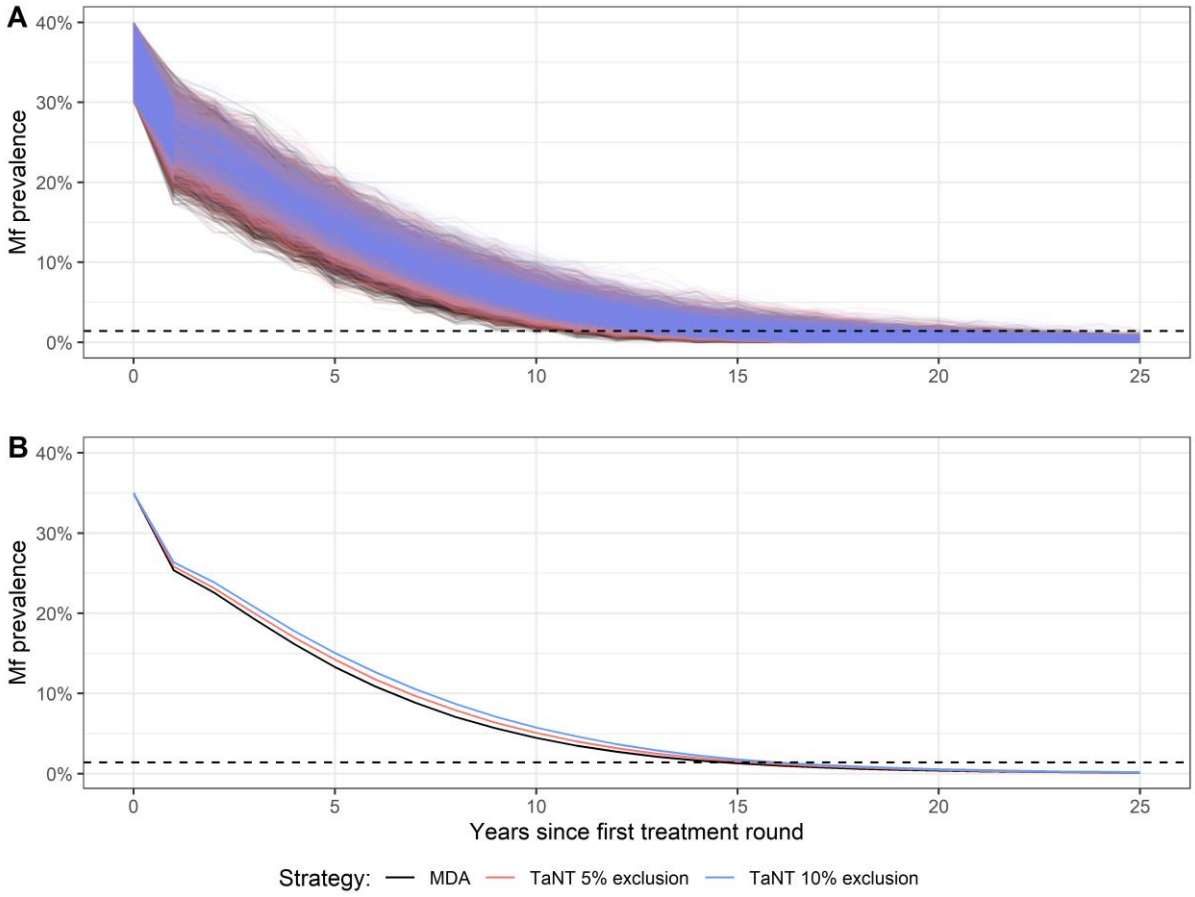

Figure 2

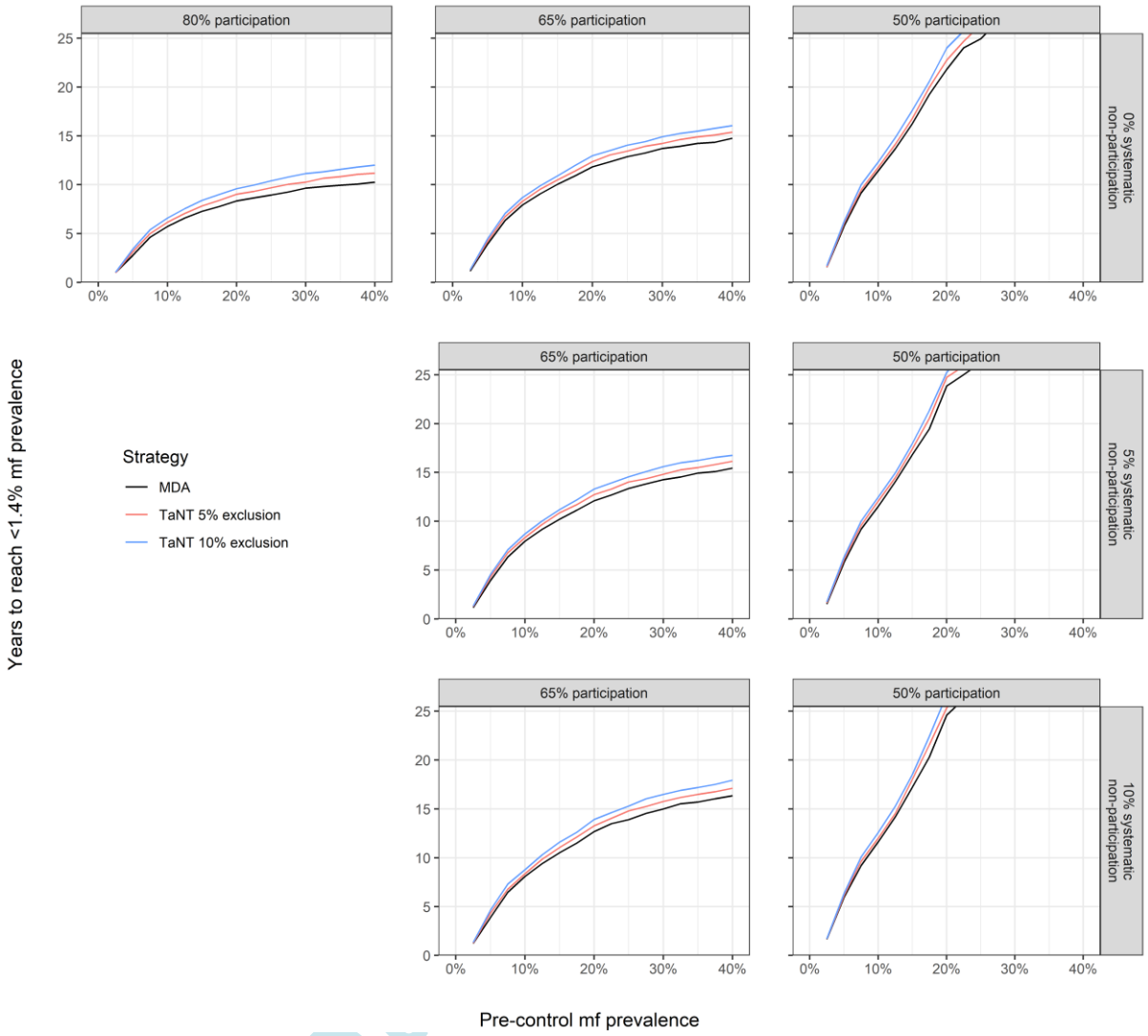

Figure 3

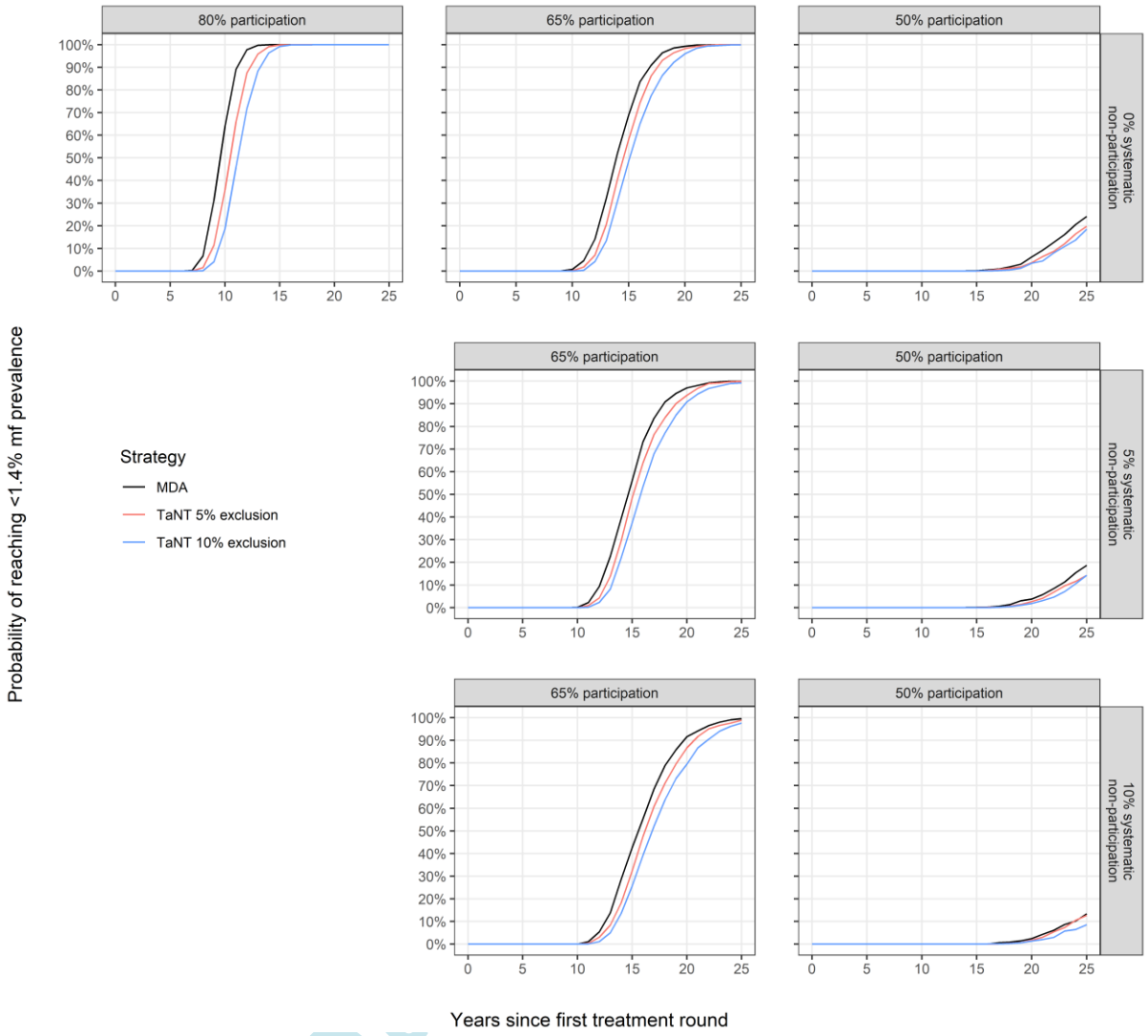

Figure 4