



# Developing Strategies for Onchocerciasis Elimination Mapping and Surveillance Through The Diagnostic Network Optimization Approach

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**Background:** Onchocerciasis (river blindness) is a filarial disease targeted for elimination of transmission. However, challenges exist to the implementation of effective diagnostic and surveillance strategies at various stages of elimination programs. To address these challenges, we used a network data analytics approach to identify optimal diagnostic scenarios for onchocerciasis elimination mapping (OEM).

**Methods:** The diagnostic network optimization (DNO) method was used to model the implementation of the old Ov16 rapid diagnostic test (RDT) and of new RDTs in development for OEM under different testing strategy scenarios with varying testing locations, test performance and disease prevalence. Environmental suitability scores (ESS) based on machine learning algorithms were developed to identify areas at risk of transmission and used to select sites for OEM in Bandundu region in the Democratic Republic of Congo (DRC) and Uige province in Angola. Test sensitivity and specificity ranges were obtained from the literature for the existing RDT, and from characteristics defined in the target product profile for the new RDTs. Sourcing and transportation policies were defined, and costing information was obtained from onchocerciasis programs. Various scenarios were created to test various state configurations. The actual demand scenarios represented the disease prevalence at IUs according to the ESS, while the counterfactual scenarios (conducted only in the DRC) are based on adapted prevalence estimates to generate prevalence close to the statistical decision thresholds (5% and 2%), to account for variability in field observations. The number of correctly classified implementation units (IUs) per scenario were estimated and key cost drivers were identified.

**Results:** In both Bandundu and Uige, the sites selected based on ESS had high predicted onchocerciasis prevalence >10%. Thus, in the actual demand scenarios in both Bandundu and Uige, the old Ov16 RDT correctly classified all 13 and 11 IUs, respectively, as requiring CDTi. In the counterfactual scenarios in Bandundu, the new RDTs with higher specificity correctly classified IUs more cost effectively. The new RDT with highest specificity (99.8%) correctly classified all 13 IUs. However, very high specificity (e.g., 99.8%) when coupled with imperfect sensitivity, can result in many false negative results (missing decisions to start MDA) at the 5% statistical decision threshold (the decision rule to start MDA). This effect can be negated by reducing the statistical decision threshold to 2%. Across all scenarios, the need for second stage sampling significantly drove program costs upwards. The best performing testing strategies with new RDTs were more expensive than testing with existing tests due to need for second stage sampling, but this was offset by the cost of incorrect classification of IUs.

**Conclusion:** The new RDTs modelled added most value in areas with variable disease prevalence, with most benefit in IUs that are near the statistical decision thresholds. Based on the evaluations in this study, DNO could be used to guide the development of new RDTs based on defined sensitivities and specificities. While test sensitivity is a minor driver of whether an IU is identified as positive, higher specificities are essential. Further, these models could be used to explore the development and optimization of new tools for other neglected tropical diseases.

**Keywords:** diagnostic network optimization, onchocerciasis, Ov16 RDT, onchocerciasis elimination mapping, river blindness

## INTRODUCTION

Onchocerciasis affects about 20.9 million people worldwide, with 99% of cases found in 31 countries in sub-Saharan Africa (1). The burden of this disease predominantly affects the poorest, most remotely located villages, with limited access to healthcare, and leads to low productivity and poor socio-economic development. The development of new diagnostic tools coupled with the effectiveness of control through community-directed treatment with ivermectin (CDTi), the elimination of onchocerciasis in 11 out of 13 foci in the Americas (2–4), and the successful interruption of transmission in many foci in Africa (5–7), led the World Health Organization (WHO) to include elimination of onchocerciasis in its roadmap for overcoming the global impact of neglected tropical diseases (NTDs) (8). The evolution of onchocerciasis management from control (in only hyper- and meso-endemic areas) to elimination (in all endemic areas) requires a more comprehensive understanding of the distribution of infection. As a result, onchocerciasis elimination mapping (OEM) needs to be undertaken in all areas not currently under treatment, to detect disease transmission and inform the implementation of CDTi (9).

For OEM it is imperative that the transmission status of all implementation units (IUs; the level at which each country determines that treatment should be conducted) is correctly identified, to avoid missing an IU requiring treatment or conducting extensive CDTi in an IU that does not require

treatment. As low levels of infection can still support the transmission of onchocerciasis, a principal challenge to OEM programs is the poor sensitivity and specificity of current diagnostics tools (9–11). WHO recommends the use of an enzyme-linked immunosorbent assay (ELISA) or rapid diagnostic test (RDT) that detects antibodies to the parasite-specific Ov16 antigen (12–14). These tests give indication of past exposure to infection and are recommended for mapping hypo-endemic areas and detecting recent transmission in children (15). While they are currently the best tools for OEM, the RDT has shown variable performance in field conditions compared with laboratory-based settings (14), and the variety of in-house protocols and kit-based ELISAs available represents challenges to feasibility of wide-scale implementation of ELISA tests. Thus, improvements to the Ov16 tests are required to enhance their suitability for OEM, and as such, a number of new diagnostic tools are under development.

It is important to consider how best to efficiently implement the use of new test formats currently in development, particularly given that the rapid epidemiological mapping for onchocerciasis (16), previously used to identify villages that may be candidates for CDTi relied on nodule palpation and skin-snip microscopy in areas with high transmission. Diagnostic network optimization (DNO) is a method used to identify the best diagnostic network configuration from a set of available alternatives by integrating multiple data inputs, such as the physical configuration and infrastructure of the diagnostic network, including the number,

locations, and capacity of facilities and testing sites, and referral linkages. Network optimization and strategic supply chain management using specialized software is common practice in the commercial sector (17), and these analytical modelling software approaches are now being applied increasingly to the optimization of diagnostic networks. The objective of network optimization is to balance the need for increased access to services with cost efficiency and feasibility of implementation in resource-constrained settings, and to help Ministries of Health identify gaps and misalignments in diagnostic service delivery that can be addressed through laboratory strengthening interventions. This approach has previously been applied to inform country-led decision-making processes for tuberculosis and HIV diagnosis (18, 19).

We adapted the DNO approach for OEM, in order to evaluate optimal implementation models based on the sensitivity and specificity of the existing Ov16 RDT. We also evaluated the impact of improved RDTs under development based on the target product profile (TPP) (20), and identified key cost drivers for the different testing strategies.

## MATERIALS AND METHODS

This study employed the DNO approach to model the implementation of the old Ov16 RDT and new Ov16 RDTs in development for OEM. Different scenarios with varying testing locations, test performance and disease prevalence were assessed. Data inputs used in the DNO model are summarized in **Figure 1**. Environmental suitability scoring (ESS) was used to select sites for OEM in areas identified as being at risk of transmission. Test sensitivity and specificity ranges were

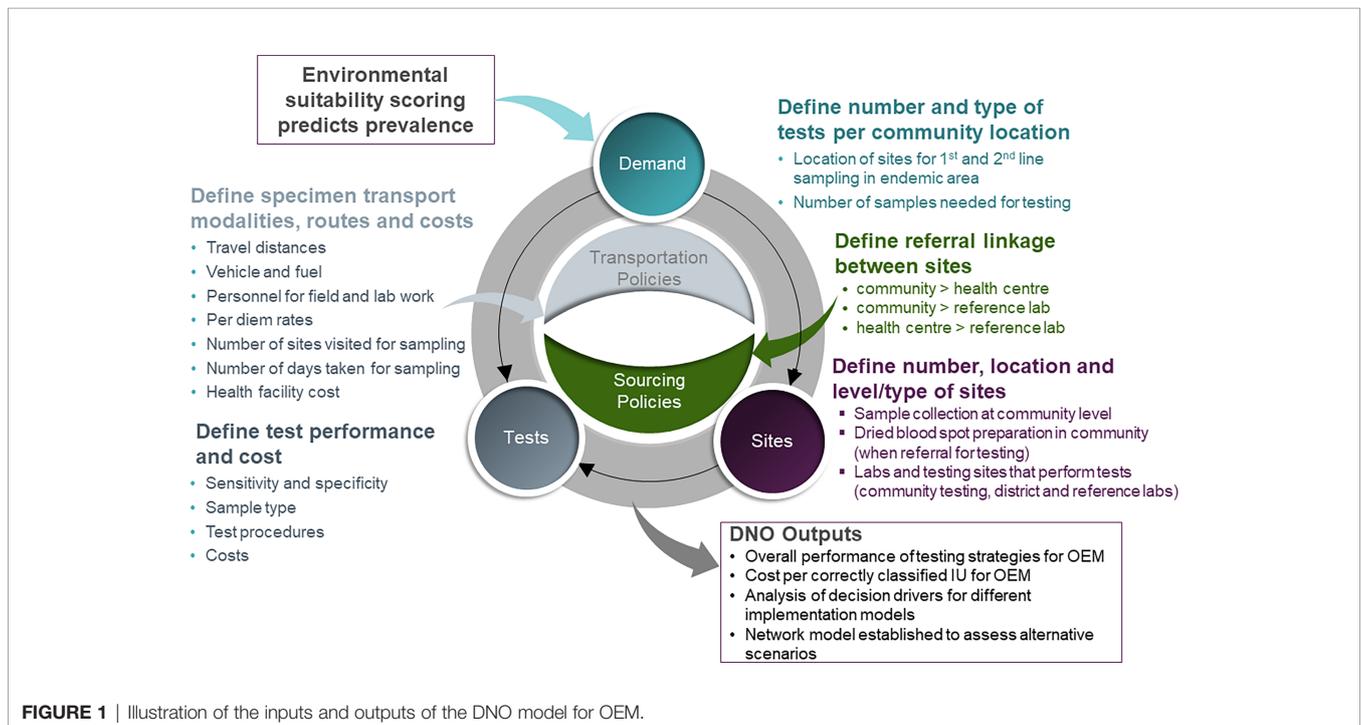
obtained from the literature for the existing RDT, and from characteristics defined in the TPP for the new tests. Information on the sourcing and transportation costs for running the activities was obtained from current onchocerciasis programs. Actual demand scenarios based on disease prevalence according to the ESS, and counterfactual scenarios based on adapted prevalence estimates to generate prevalence close to the statistical decision thresholds, were assessed to account for variability in field observations. Based on the results, the overall performance of testing strategies for OEM, the cost per correctly classified IU, and the decision drivers for different implementation models, all using current and improved tests, were determined.

## Data Inputs

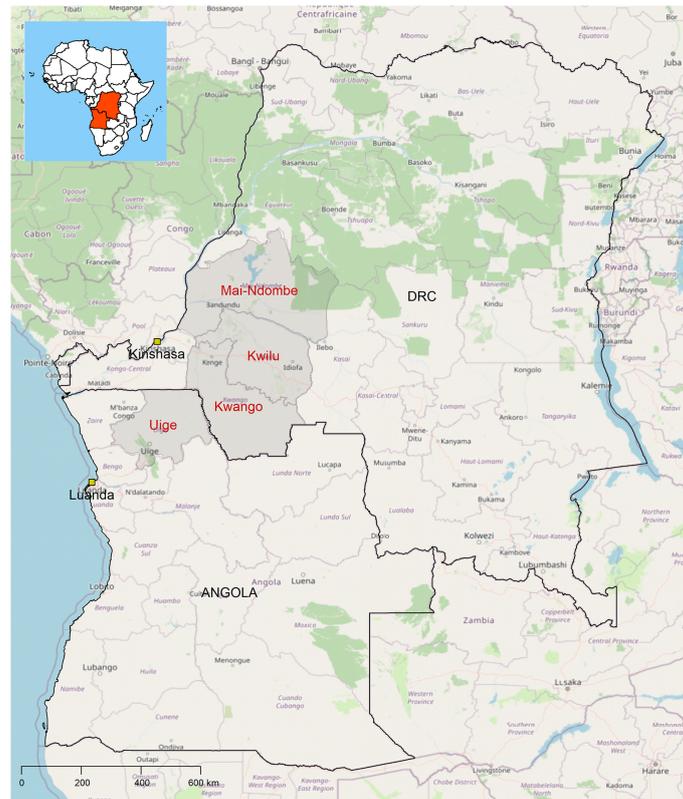
The DNO model included three main data inputs. First, the demand for testing informed the locations of the sites and testing procedures. Second, data on the tests, including performance, sample collection, number and type of tests required, testing procedures and cost. Third, sourcing and transportation policies to define the relationships between locations and testing sites. The data for the study were compiled from various sources including questionnaires administered to onchocerciasis program personnel (**Supplementary File S1**) and the ESS.

## Sample Collection Site Selection

This work focused on regions in the Democratic Republic of Congo (DRC) and Angola requiring OEM. Following review of onchocerciasis data available on the ESPEN portal (21), the Bandundu region of DRC, with IUs in Kwilu, Kwango and Mayi Ndombe provinces (N=13), and the IUs in Uige province of Angola (N=11), were selected for inclusion (**Figure 2**).



**FIGURE 1** | Illustration of the inputs and outputs of the DNO model for OEM.



**FIGURE 2** | Maps of Angola (left) and the Democratic Republic of Congo (right) showing the study provinces included in the analysis.

To enable the selection of villages based on suitability for OEM at a given settlement, we employed ESS as a proxy for the current strategy for OEM. The current strategy recommends a two-step approach for identification of sites in need of treatment in each IU (14). The first step is the purposeful selection of five first line or high-risk villages and sampling of 100 adults per village to determine the prevalence of onchocerciasis using the Ov16 RDT. If the prevalence is  $\geq 5\%$  statistical threshold (the decision rule to start MDA) in one or more villages, CDTi is recommended for the IU. If the prevalence is  $< 5\%$  in all five first line villages, second stage sampling is required. For this second step, villages are ordered geographically, and 20 villages are systematically selected. Fifty adults are sampled and tested and if the prevalence is  $\geq 5\%$  in two or more villages or  $\geq 10\%$  in one village, CDTi is recommended. Otherwise, no treatment is needed in the IU (14). For the DNO analysis, ESS was used for the selection of the frontline villages as well as for the 20 villages if second stage sampling was indicated.

An ensemble of machine learning modelling algorithms was used to develop a high-resolution map of ESS for onchocerciasis. In this application the ensemble machine learning modelling approach (22) was based on 6 classification algorithms within the Biodiversity Modelling (BIOMOD) computational framework for modelling species distribution (23) (namely: random forest (RF), boosted regression trees (GBM), generalized linear

regression (with quadratic terms for all predictors) (GLM), generalized additive models (GAM), artificial neural network (ANN) and multiple adaptive regression splines (MARS)) and using an array of environmental variables (predictors relating to climate, topography, human factors and hydrology, with selection of final predictors made using principal component analysis to reduce dimensionality) (24) against observed onchocerciasis survey data in the ESPEN data portal (21) to obtain the predicted environmental suitability score (and probability of occurrence) and binary occurrence of onchocerciasis using a cut-off that maximized sensitivity, specificity and proportion of IUs correctly classified. In this application the random forest approach outperformed the other algorithms tested (**Supplementary File S2**) (25). The final ensemble was constructed using a weighted mean of probability approach. Individual models were weighted based on their performance (receiver operating characteristic (ROC) statistic and the Hanssen-Kuipers discriminant (also known as true skill statistic, TSS) (26). Only models with ROC  $> 0.7$  through internal validation were included). We obtained predicted environmental suitability model (probability of occurrence) and final binary occurrence map using a cut-off that maximized sensitivity, specificity and PCC (proportion correctly classified). The prevalence of occurrence was bivariate, estimated against the ESS to provide a measure of

prevalence at a given ESS value for the purposes of the settlement sampling. In addition, the estimates from the ESS score were externally validated using recent survey data from Malawi and Burundi which were not included in the original input data to compare observed prevalence against the predicted prevalence based on ESS (Figure 3). The ESS analyses were conducted in R using the biomod2 package (27). For all prevalence estimates, the 95% confidence intervals are provided.

### Testing Site Selection

Sample collection locations (villages identified using the ESS) and testing laboratories (28) were incorporated into the model. Some sites within the model included both referring and referral capacity, e.g., where sample collection and testing are performed in the community. Some sites required laboratory testing at the nearest district level hospital (28). These sites were linked for referral of samples for testing per the sourcing policies and transportation policies (described below). Site information included site type (facility or community), services available (sample collection, preparation and testing of dried blood spots [DBS]), capacity for service delivery, and geographic coordinate system (GIS) coordinates.

### Diagnostic Tests

Product demand (i.e., the number of tests required) denoted the tests (or processes) required for OEM, and location of demand was split by sample collection, DBS or direct testing of blood in the community, and was expressed by test type, and estimated at each unique location (community or facility). Instrument costs and capacity constraints were included to ensure the results of the model accurately represent the realities of operating the diagnostic testing services within the network. Test performance parameters included in the model are shown in Table 1.

### Sourcing and Transportation Policies

Sourcing policies define the relationships within the network model between referring locations and the referral testing sites that

**TABLE 1** | Performance parameters of existing and new tests used for OEM.

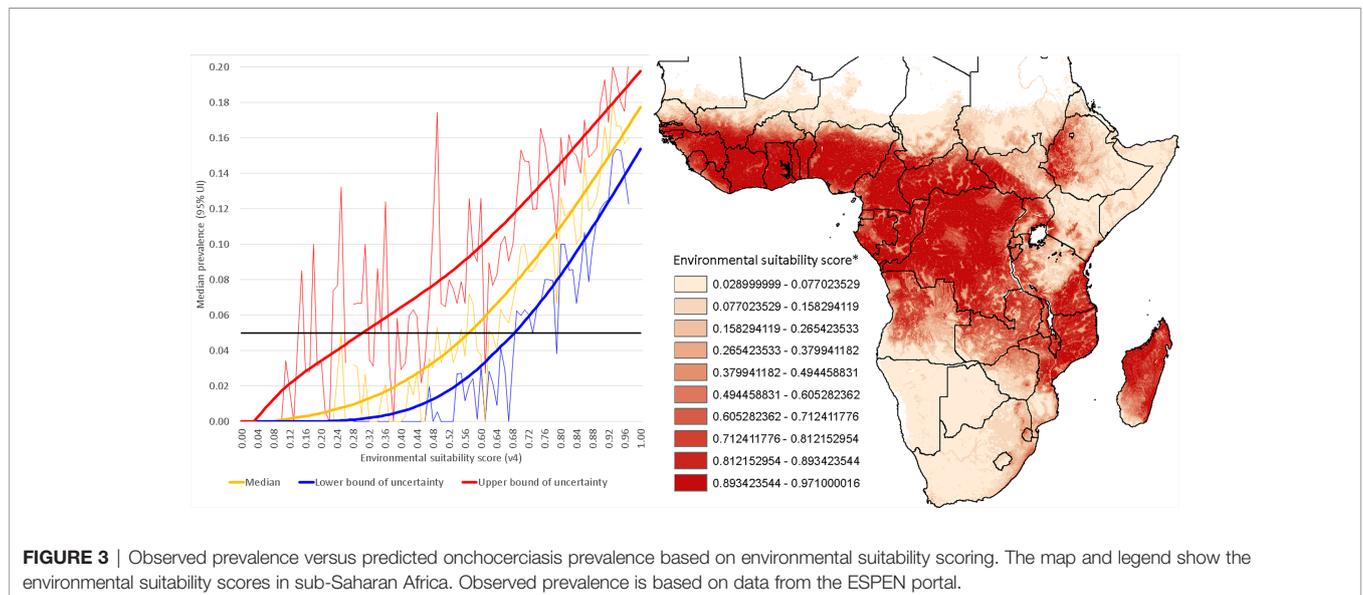
RDT	
<b>Existing tests</b>	<b>Range tested**:</b> <b>Sensitivity:</b> 80–95% <b>Specificity:</b> 95–100% <b>Modelled parameters:</b> 87.5% sensitivity/97.5% specificity 80% sensitivity/95% specificity
<b>New tests*</b>	<b>Range tested**:</b> <b>Sensitivity:</b> 85–95% (same as above) <b>Specificity:</b> 98% or 99.8% <b>Modelled parameters:</b> 85% sensitivity/98% or 99.8% specificity 90% sensitivity/98% or 99.8% specificity 95% sensitivity/98% or 99.8% specificity

*New test performance characteristics are based on consensus target product profiles (20).*

*\*\*The performance of old tests has been shown to vary under routine implementation across settings (29–31). Therefore, a limited range of sensitivity and specificity parameters was tested.*

*\*60–99.8% specificity is not feasible, mid-point of 80% would equate to 20% false positivity and would lead to blanket MDA decision regardless of underlying prevalence. Therefore, analysis restricted to the RDT specificity range.*

perform the testing. Transportation policies define the actual route and mechanism by which samples travel from testing sites to referring facilities. For estimating distances between primary health care centers and district health facilities, actual distances were used where available (for existing transportation routes). Where actual distances between facilities and testing sites were not available, a distance adjustment factor was computed based on actual compared with straight line distances on the map for known transport lanes in the same district or region. For estimating unknown actual distances, the straight-line distance was multiplied by the average transport adjustment factor. Each transportation mode (e.g., motorbike, car, bus, courier service, human carrier etc.) is represented as a transportation policy. Each sourcing policy requires a corresponding transportation policy.



**FIGURE 3** | Observed prevalence versus predicted onchocerciasis prevalence based on environmental suitability scoring. The map and legend show the environmental suitability scores in sub-Saharan Africa. Observed prevalence is based on data from the ESPEN portal.

## Diagnostic Network Optimization Modelling

The diagnostic network model was constructed using commercial supply chain management design software, Supply Chain Guru<sup>®</sup> 8.4 (SCG) (LLamasoft, Inc, Ann Arbor, MI). Data sources used to populate the model are shown in **Supplementary File S3**. These files were reviewed for completeness, plausibility and internal consistency of inputs, and were confirmed with the country Onchocerciasis program teams, before being merged and formatted into the SCG software's model database schema. Various scenarios were created to test various state configurations for the network (**Table 2**). Scenarios 1.1 and 2.1 represent direct testing of the current Ov16 RDT in the community, which has been shown to produce poorer performance compared with testing in the laboratory (14). Scenarios 1.2/1.3 and 2.2/2.3 represent the recommended testing strategy for OEM [community sampling and DBS preparation, followed by DBS referral for RDT testing in a laboratory (14)]. The actual demand scenarios represent the disease prevalence at IUs according to the ESS (**Supplementary File S4**). The counterfactual demand scenarios 2.1/2.2/2.3/2.4 (conducted only in the DRC) are based on adapted prevalence estimates to generate prevalence close to the decision thresholds (5% statistical threshold for initiating CDTi, and 2% biological threshold [break point below which transmission cannot be sustained] (14) in some IUs, to account for variability in field observations (**Supplementary File S5**).

### Cost Analysis

Cost analysis was performed on the incremental cost components that varied between scenarios. Thus, we did not consider complete program level costs as it was assumed that these would not vary between scenarios. The following costs were included:

1. The test cost (32)
2. The number of secondary screening rounds required (determined by the test performance parameters and village prevalences) (**Table 1**)
3. Human resource costs based on the numbers of days that different individuals remain in the field
4. Transport costs to and within the field
5. Field facilitation costs (including fees paid to supporting health facilities)
6. Human resource costs for processing samples.

Unless otherwise specified the costs were compiled in consultation with colleagues in the DRC and Angola and from relevant published literature (**Supplementary File S1**) and checked against other publications (33, 34). Costs are broken down in detail in **Supplementary File S3**.

## RESULTS

### ESS and Route Mapping

The estimates from the best performing machine learning model suggested a high environmental suitability for Onchocerciasis across much of the DRC, with implied onchocerciasis prevalence of >2%. In Angola, the environmental suitability was highly variable, with a wide range of implied onchocerciasis prevalence from 0 to 15% (**Figure 4**). However, the sites selected for OEM using the ESS in DRC and Angola had high predicted onchocerciasis prevalence >10% (**Supplementary Information S4**). Based on the sites selected through the ESS, it was possible to predefine the most optimum and cost-effective travel routes for site visits and sample collection depending on the procedures employed by the country onchocerciasis program (**Figure 5**). Route mapping based on network modelling showed that a maximum of 10 days was required for OEM in each IU.

### Actual Scenarios

Scenarios 1.1 and 2.1 were considered in preliminary analysis (old RDT with community testing). However, given inadequate performance of current tests in the community (14), these scenarios were excluded from final analysis and are not presented here. In the actual demand scenarios 1.2 and 1.3, in both Bandundu in DRC and Uige in Angola, both old and new Ov16 RDTs correctly classified all IUs based on the first stage sampling only, as the point prevalence estimates for onchocerciasis, based on ESS, were high (>10%) [**Supplementary Information S4**].

### Counterfactual Scenarios and Sensitivity/ Specificity Analysis

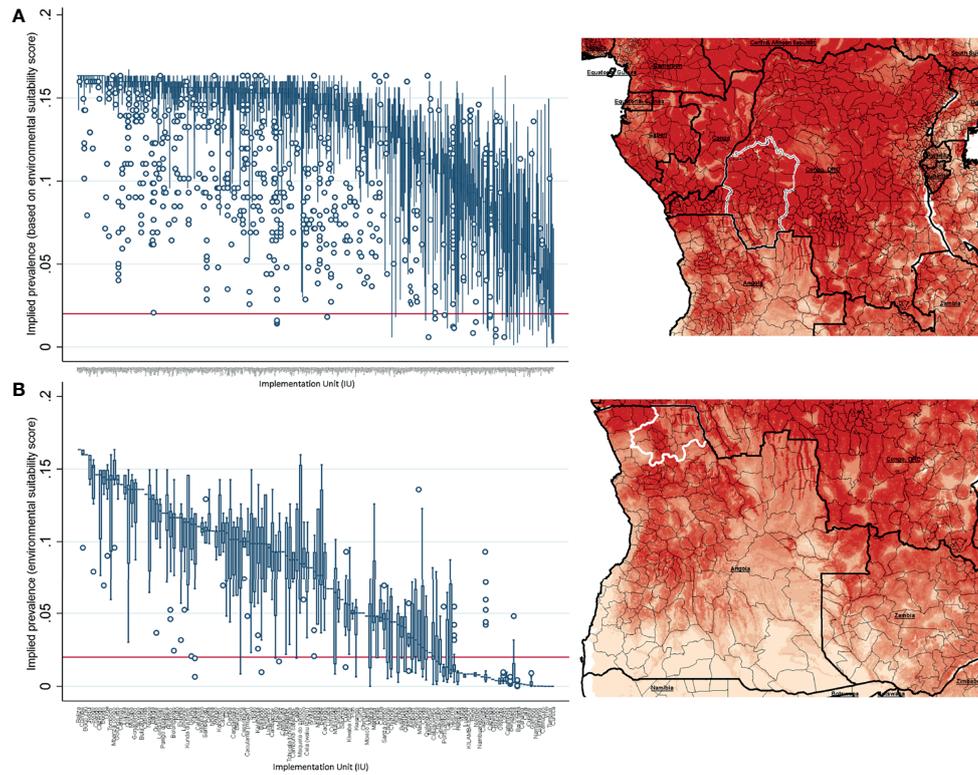
In the counterfactual demand scenarios, we modelled the performance of the old and new Ov16 RDTs with the sensitivity and specificity values provided in **Table 1**.

Assuming test performance of 87.5% sensitivity and 97.5% specificity, the old Ov16 RDT (scenario 2.2) enabled correct identification of 12/13 IUs in Bandundu, with a 92% accuracy

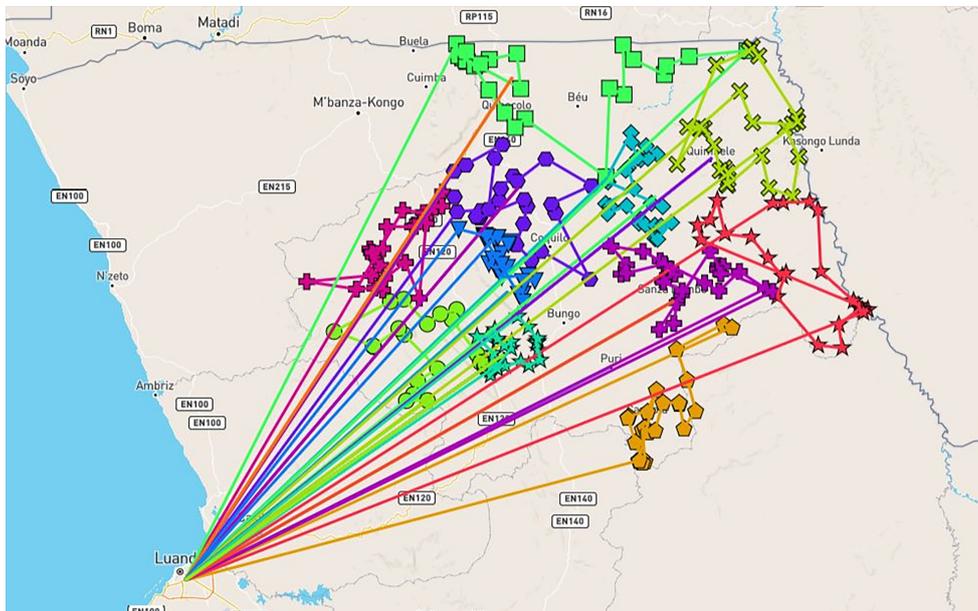
**TABLE 2** | Scenarios investigated in the models.

Scenario Class	Scenario	Description
<b>ACTUAL DEMAND</b>	Scenario 1.1	Community sampling and old RDT testing
	Scenario 1.2	Community sampling and preparation of DBS for referral for old RDT testing at HF (general reference hospital)
	Scenario 1.3	Community sampling and new RDT at HF (general reference hospital)
<b>COUNTERFACTUAL DEMAND</b>	Scenario 2.1	Community sampling and old RDT testing
	Scenario 2.2	Community sampling and preparation of DBS for referral for old RDT testing at HF (general reference hospital)
	Scenario 2.3	Community sampling and new RDT at HF (general reference hospital)
	Scenario 2.4	Community sampling and testing with new RDT

Actual demand was determined using environmental suitability score to predict prevalence at IUs. Counterfactual demand used adapted prevalence estimates to generate prevalence close to 5% or 2% statistical decision threshold in some IUs. DBS, dried blood spot; HF, health facility; RDT, rapid diagnostic test.



**FIGURE 4** | Environmental suitability and predicted onchocerciasis prevalence in **(A)** the Democratic Republic of Congo and **(B)** Angola.



**FIGURE 5** | Travel routes based on sites selected using environmental suitability scores in Uige province, Angola. This assumes a return to Luanda after a visit to each IU. The figure is illustrative only, since second stage sampling was not required for any IUs in Uige province based on actual demand.

(Table 3). Eight IUs were correctly classified at first stage sampling, and five required a second stage sampling, of which four were then correctly classified and one resulted in an incorrect decision to start CDTi. When the sensitivity and specificity were lowered to 80% and 95% respectively, the RDT resulted in a 69% accuracy with the first stage sampling leading to the decision to start CDTi in all 13 IUs (9 correct and 4 incorrect decisions).

We also evaluated the performance of the new RDTs (scenario 2.3) with improved specificities. A new RDT with

98% specificity enabled correct identification of 12/13 IUs in Bandundu (Table 4), with a 92% accuracy. One start CDTi decision is missed at first stage sampling and one overall decision is incorrect (irrespective of test sensitivity). All no CDTi decisions required a second stage sampling, with the correct decisions made. On the other hand, assuming a new RDT with 99.8% specificity enabled the correct identification of all IUs (100% accuracy). All start CDTi decisions can be made at first stage sampling, and all no CDTi decisions require a second stage sampling.

TABLE 3 | Impact of test sensitivity and specificity on correct classification of IUs based old RDTs in Bandundu, DRC.

IU	Prevalence	Correct IU level decision	% positivity based on Old RDT with varying performance		First stage decision		Second stage decision	
			87.5% se/97.5% sp	80% se/95% sp	87.5% se/97.5% sp	80% se/95% sp	87.5% se/97.5% sp	80% se/95% sp
			Inongo	10.5%	CDTi	11%	13%	CDTi
Kingandu	7.5%	CDTi	9%	11%	CDTi	CDTi	N/A	N/A
Kajiji	6.5%	CDTi	8%	10%	CDTi	CDTi	N/A	N/A
Kahemba	5.9%	CDTi	7%	9%	CDTi	CDTi	N/A	N/A
Kikwit-Nord	4.9%	CDTi	7%	8%	CDTi	CDTi	N/A	N/A
Pay Kongila	5.0%	CDTi	7%	9%	CDTi	CDTi	N/A	N/A
Kikwit-Sud	4.5%	CDTi	6%	8%	CDTi	CDTi	N/A	N/A
Kwango	2.0%	No CDTi	4%	6%	2 <sup>nd</sup> stage	CDTi*	No CDTi	N/A
Masi	3.8%	CDTi	6%	8%	CDTi	CDTi	N/A	N/A
Manimba								
Mosango	1.2%	No CDTi	3%	6%	2 <sup>nd</sup> stage	CDTi*	No CDTi	N/A
Mungindu	2.5%	CDTi	4%	7%	2 <sup>nd</sup> stage	CDTi	No CDTi*	N/A
Sia	1.6%	No CDTi	4%	6%	2 <sup>nd</sup> stage	CDTi*	No CDTi	N/A
Vanga	0.6%	No CDTi	3%	5%	2 <sup>nd</sup> stage	CDTi*	No CDTi	N/A

\*Represent the incorrect decisions. CDTi, community-directed treatment with ivermectin; IU, implementation unit; Se, sensitivity; Sp, specificity.

TABLE 4 | Impact of test specificity on correct classification of IUs based new RDTs in Bandundu, DRC.

IU	Prevalence	Correct IU level decision	98% specificity						99.8% specificity					
			Sensitivity			First stage decision at 5% statistical decision threshold	Second stage decision	Sensitivity			First stage decision at 2% threshold	Second stage decision		
			85	90	95			85	90	95				
			% positivity			% positivity								
Inongo	10.5%	CDTi	11%	11%	12%	CDTi	N/A	9%	9%	10%	CDTi	N/A		
Kingandu	7.5%	CDTi	8%	8%	9%	CDTi	N/A	6%	7%	7%	CDTi	N/A		
Kajiji	6.5%	CDTi	8%	7%	8%	CDTi	N/A	6%	5%	6%	CDTi	N/A		
Kahemba	5.9%	CDTi	7%	7%	7%	CDTi	N/A	5%	5%	6%	CDTi	N/A		
Kikwit-Nord	4.9%	CDTi	6%	6%	6%	CDTi	N/A	4%	4%	5%	CDTi	N/A		
Pay Kongila	5.0%	CDTi	6%	6%	6%	CDTi	N/A	4%	5%	5%	CDTi	N/A		
Kikwit-Sud	4.5%	CDTi	6%	6%	6%	CDTi	N/A	4%	4%	4%	CDTi	N/A		
Kwango	2.0%	No CDTi	4%	4%	4%	2 <sup>nd</sup> stage	No CDTi	2%	2%	2%	2 <sup>nd</sup> stage	No CDTi		
Masi	3.8%	CDTi	5%	5%	5%	CDTi	N/A	3%	3%	4%	CDTi	N/A		
Manimba														
Mosango	1.2%	No CDTi	3%	3%	3%	2 <sup>nd</sup> stage	No CDTi	1%	1%	1%	2 <sup>nd</sup> stage	No CDTi		
Mungindu	2.5%	CDTi	4%	4%	4%	2 <sup>nd</sup> stage	No CDTi*	2%	2%	2%	CDTi	N/A		
Sia	1.6%	No CDTi	3%	3%	3%	2 <sup>nd</sup> stage	No CDTi	1%	1%	2%	2 <sup>nd</sup> stage	No CDTi		
Vanga	0.6%	No CDTi	2%	2%	2%	2 <sup>nd</sup> stage	No CDTi	0%	0%	1%	2 <sup>nd</sup> stage	No CDTi		

\*Represent the incorrect decisions. CDTi, community-directed treatment with ivermectin; IU, implementation unit.

We further tested the decision-making process based on RDTs (both old and new) with different sensitivities and specificities, tested in the laboratory or community (Table 5). In scenario 2.2 in which samples are tested in a laboratory facility, the old RDT with 80% sensitivity and 95% specificity resulted in all 13 IUs being classified as requiring CDTi based on first stage sampling. However only 9 IUs truly required CDTi. The incorrect classification of 4 IUs as requiring CDTi resulted in costs above USD \$1M to the program. In scenarios 2.3 and 2.4, where the sensitivity of a new RDT was between 85% and 95% with a specificity of 98% (with testing performed either in the community or laboratory), 8 IUs were correctly classified as requiring CDTi based on first stage sampling. The remaining 5 IUs required second stage sampling, out of which 4 IUs were correctly classified as not requiring CDTi (92% accuracy, irrespective of test sensitivity). When the specificity of the new RDT is increased to 99.8%, all 13 IUs were correctly classified.

However, 4 IUs required second stage sampling. All CDTi decisions can be made during first line sampling, and all no CDTi decisions required second stage sampling. Nonetheless, very high specificity (e.g., 99.8%) when coupled with imperfect sensitivity, can result in many false negative results (missing decisions to start MDA) at the 5% statistical decision threshold. This effect can be negated by reducing the statistical decision threshold to 2%.

### Cost Drivers

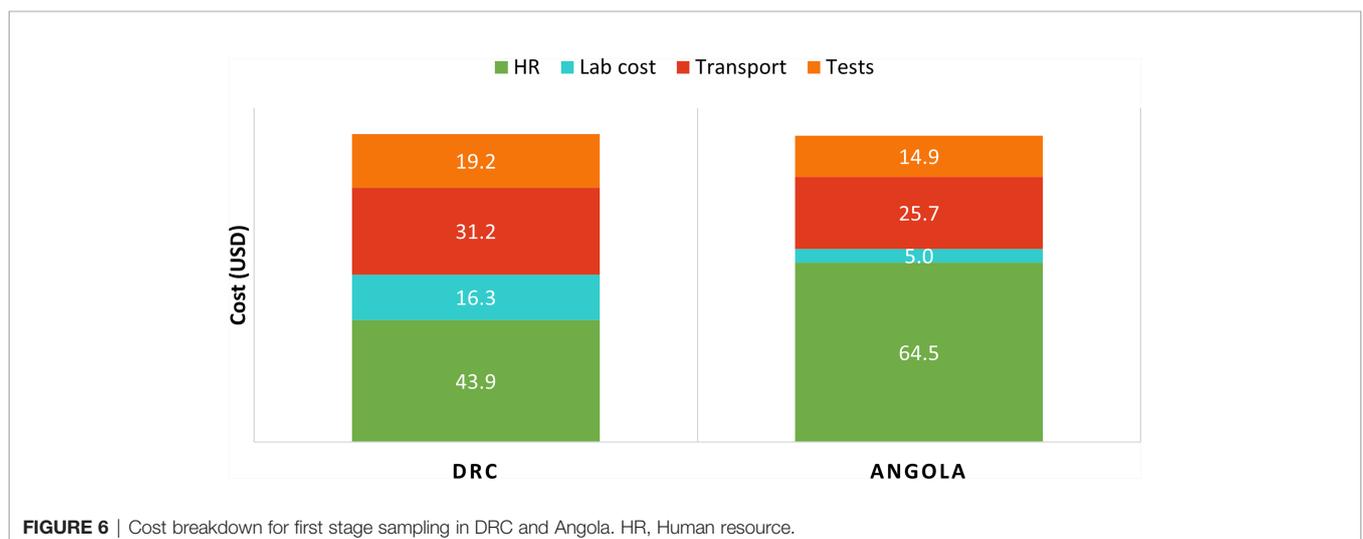
The number of tests performed, and the time spent in the field by the survey team in terms of transportation and human resource were the key cost drivers. In DRC, the tests, transportation, laboratory and human resource costs represented 19.2%, 31.2%, 16.3% and 43.9% of the total costs, respectively (Figure 6). In Angola, the corresponding values were 14.9%, 25.7%, 5.0% and 64.5%. Variation in overall cost across countries was minimal.

**TABLE 5 |** Impact of test performance on correct classification of IUs based on laboratory or community testing in Bandundu, DRC (in counterfactual scenario).

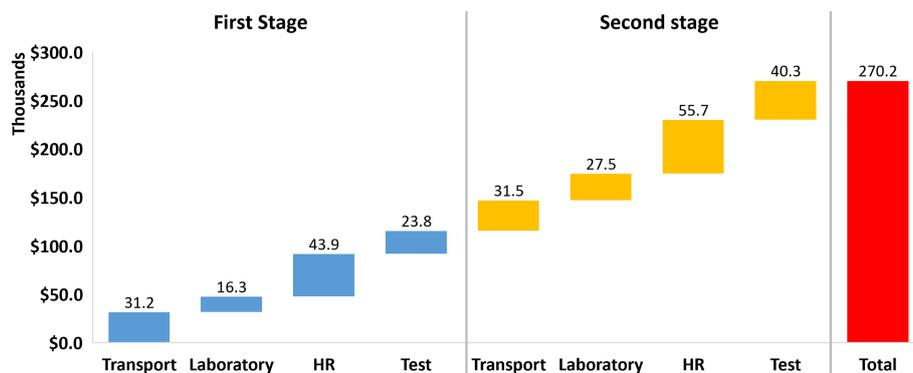
Test performance	Old RDT(80% se, 95% sp)		New RDT(85–95% se, 98% sp)		New RDT(85–95% se, 99.8% sp)	
	District Lab (scenario 2.2)	District Lab (scenario 2.3)	Community (scenario 2.4)	District Lab (scenario 2.3)	Community (scenario 2.4)	
No. of IUs	13	13	13	13	13	
No. of IUs wrongly classified as no CDTi	0	1	1	0	0	
No. of IUs wrongly classified as start CDTi	4	0	0	0	0	
No. of IUs correctly classified as no CDTi	0	4	4	4	4	
No. of IUs correctly classified as start CDTi	9	8*	8*	9	9	
Total correctly classified IUs	9/13	12/13	12/13	13/13	13/13	
Sampling required (no. IUs)	1 <sup>st</sup> stage – 13 2 <sup>nd</sup> stage – 0	1 <sup>st</sup> stage – 13 2 <sup>nd</sup> stage – 5	1 <sup>st</sup> stage – 13 2 <sup>nd</sup> stage – 5	1 <sup>st</sup> stage – 13 2 <sup>nd</sup> stage – 4	1 <sup>st</sup> stage – 13 2 <sup>nd</sup> stage – 4	
Overall cost (USD)	110,700	185,100	178,700	171,000	165,800	
Cost per correctly classified IU (USD)	12,300	15,425	14,892	13,154	12,754	
Cost of incorrect CDTi initiation (estimated. 10-year treatment cost for 4 IUs)	1,172,410	–	–	–	–	

\*Public health impact of not starting MDA in endemic area. CDTi, community-directed treatment with ivermectin; IU, implementation unit; RDT, rapid diagnostic test; Se, sensitivity; Sp, specificity; USD, United States dollars.

The colors represent the accuracy of the classification. Red = less accurate (9/13). Green = very accurate (13/13).



**FIGURE 6 |** Cost breakdown for first stage sampling in DRC and Angola. HR, Human resource.



**FIGURE 7** | Cost breakdown for a new RDT with 99.8% specificity, with testing performed in the laboratory. In this scenario, second stage sampling is required in 4 IUs. The laboratory costs represent the additional personnel costs for running the samples, as well as support costs to the facility. HR, Human resource.

Second stage sampling (undertaken only in the counterfactual scenarios in DRC) represented over 50% of costs. The implementation costs of new RDTs were moderately higher than that of the old RDT. **Figure 7** represents the estimated cost breakdown for a new RDT with 99.8% specificity, with testing performed in the laboratory. Costs of testing the new RDTs in the community were slightly lower than testing at a laboratory facility (**Table 5**).

## DISCUSSION

This study aimed to evaluate the optimal use of the old Ov16 RDT for OEM. It also aimed to assess the impacts of improved diagnostic tools as recommended in target product profiles for the development of new tools for onchocerciasis (20). The results show that investment in new tests and design of context-specific implementation models are important to reduce costs and improve effectiveness of OEM, reducing both cost of testing and cost of unnecessary CDTi. Our evaluations also demonstrated that new RDTs will have greatest impact in areas with varying prevalence below and above 2%. However, these tests will be less useful in areas where the prevalence is uniformly above 5%. Where new tests with high specificity and imperfect sensitivity require lowering the statistical decision threshold to 2%, a reassessment of the statistical and biological threshold cut-offs recommended by the WHO onchocerciasis technical advisory subgroup (OTS) (14) will be warranted.

Environmental suitability and geospatial modelling scores predicting areas with the likelihood of onchocerciasis prevalence have been useful in defining areas requiring testing, and in selection of villages for first stage and second stage sampling as recommended by WHO (14). Model based predictions of onchocerciasis prevalence based on environmental predictors have been shown to be comparable with epidemiological mapping efforts to identify areas of transmission (35), and may be extended to areas with little or no available data. In Angola, the ESS was observed to be highly

variable, with implied onchocerciasis prevalence ranging from 0 to 15%. On the other hand, in DRC the ESS was high, with implied prevalence >2%. These estimates of demand in DRC and Angola were shown to be representative of actual prevalence data, allowing generalizability of results. It could be argued that actual field evaluations may be required to ascertain the range of prevalence observed, especially given the reduction in the country following years of treatment. However, the ESS approach enables a desk assessment without the need for costly field visits. The use of ESS also allows for alternate sampling strategies such as truncated sampling (**Supplementary File S1**), once the initial field data or statistical decision thresholds from the first and second stage sampling indicate the need to start CDTi. Further exploration of these strategies is warranted.

The actual demand scenario enabled the correct classification of IUs based on the old Ov16 RDT. In both Bandundu in DRC and Uige in Angola, the old Ov16 RDT correctly classified all 13 and 11 IUs, respectively, based on the first stage villages. However, this was likely due to the uniformly high prevalence in these IUs (point prevalence estimates >10%). Thus, no difference in decisions were observed across low, medium and high-performance parameters for the old RDT. Nonetheless, the performance of old tests has been shown to vary under routine implementation across settings (29–31). Based on the results presented in **Table 5**, the old RDT with lower test performance may result in lower field costs by neglecting the need for second stage sampling. However, this is offset by the high operational cost to the program as a result of the incorrect treatment of villages for several years. On the other hand, new RDTs with very high specificities will result in correct decisions in all IUs, albeit with slightly higher testing costs resulting from the need for second stage sampling in some IUs. Improved specificity reduces the probability of incorrect decision and subsequent errors in treatment. These results show that varying and inconsistent RDT sensitivity and specificity within expected bounds could have a substantial impact on treatment decisions. Test performance therefore becomes an important differentiator for correct treatment decision with prevalence close to the statistical decision threshold.

The current TPPs for onchocerciasis RDTs for mapping require sensitivities > 60% and very high specificities above 99.8% (20). Our results show that improved specificity reduces the probability of incorrect treatment decisions. Also, tests with improved performance will add most value in areas with variable disease prevalence in select IUs that are near the statistical decision thresholds. However, very high specificity (e.g., 99.8%) when coupled with imperfect sensitivity, can result in many false negative results (missed decisions to start CDTi) at the 5% statistical decision threshold. New tests must therefore have acceptable suitability for use in OEM programs.

The number of tests performed, and the number of days spent in the field in terms of the transportation and personnel costs were the major key cost drivers of all testing strategies evaluated. As such, direct testing in the community was slightly cheaper than testing at laboratory facilities, presumably due to the additional cost of collecting dried blood spots and personnel cost at the testing facilities. However, it should be noted that evaluations of the old Ov16 RDT have shown improved performance when tested in the laboratory setting compared with use in the field (14).

From our findings, the best performing testing strategies with new RDTs are more expensive than testing with existing tests with poorer performance, due to the need for second stage sampling. In terms of cost effectiveness of existing or new RDTs, the need for second stage sampling drove overall OEM testing costs. The savings on second stage sampling are due to reduced time and personnel cost being spent in the field, lower travel costs with fewer villages to visit and lower testing costs as fewer people are tested. However, second stage sampling costs are significantly outweighed by cost savings of avoiding incorrect start CDTi decisions. Assuming US \$0.5 as the CDTi cost per person (36–38), an overall cost saving of approximately US\$117,000 per annum can be made for 4 IUs with incorrect CDTi decisions. This amounts to over US\$1.17 million during a 10-year treatment period. Further, the public health impacts will be low to negligible, despite the possibility of treating some individuals who may be infected in those IUs.

## Data Limitations

As both DRC and Angola are yet to undertake any OEM activities using the old Ov16 RDT, assumptions were made on the number of personnel, approximate travel distance, vehicle hire and cost, and testing costs, based on information on previous activities focusing on surveillance and mapping using skin-snip microscopy and nodule palpation provided by the onchocerciasis programs. Assumptions were also made based on WHO recommendations for OEM. Due to the selection of the sites using the ESS and the remoteness of onchocerciasis endemic villages, poor road networks and community scattering may also affect the accessibility and number of villages reached per day, thus impacting the time spent by the teams in the field. As such, while the average cost is presented per IU, the actual cost estimations may vary during field implementation. Nonetheless, there is no reason to assume that the costs reported for the IUs included in this study are not representative.

The 5% statistical decision threshold used in this study is a provisional recommendation of the WHO OTS (14). This was based on the trade-off between sample sizes, test specificity and the

likelihood of identifying high numbers of false positives and wrongly classifying IUs as requiring MDA. The OTS acknowledges the need for this threshold to be validated or adjusted. As such, the accuracy of classification of IUs based on new Ov16 RDTs may differ depending on their confirmed specificity in the field, and the final approved thresholds for initiating MDA.

## CONCLUSION

In conclusion, the use of DNO for onchocerciasis has shown that country data can be better harnessed to inform investment in field implementation strategies, new tests and design of context-specific implementation models, to reduce costs and improve effectiveness of OEM, as well as avoid the cost of unnecessary CDTi treatment. Further, new tests as recommended by the TPPs will have greatest impact in areas with varying prevalence below or above 2%, but with less value where prevalence is above 5%. Finally, network optimization models could be useful for evaluating alternate sampling strategies to bring opportunities for cost savings. Further, these models could be used to explore the development and optimization of new tools for other NTDs such as lymphatic filariasis and visceral leishmaniasis.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

HA, DS, and JN conceived the study. SK, DM, NU, and MC provided the data. BS, PB, SR, KG, RP, and HA analysed the data. DS wrote the first draft. HA, BS, PB, DS, SR, KG, SK, JN, RP, DM, MC, and NU reviewed the paper and approved its publication. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/ftd.2021.707752/full#supplementary-material>

**Supplementary File S1** | Data requirements for network optimization modelling.

**Supplementary File S2** | Environmental suitability model selection.

**Supplementary File S3** | Cost and parameter inputs used for costing analysis.

**Supplementary File S4** | Observed prevalence versus predicted onchocerciasis prevalence based on environmental suitability scoring (actual demand scenarios).

**Supplementary File S5** | Observed prevalence versus predicted onchocerciasis prevalence based on environmental suitability scoring (counterfactual demand scenarios).

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