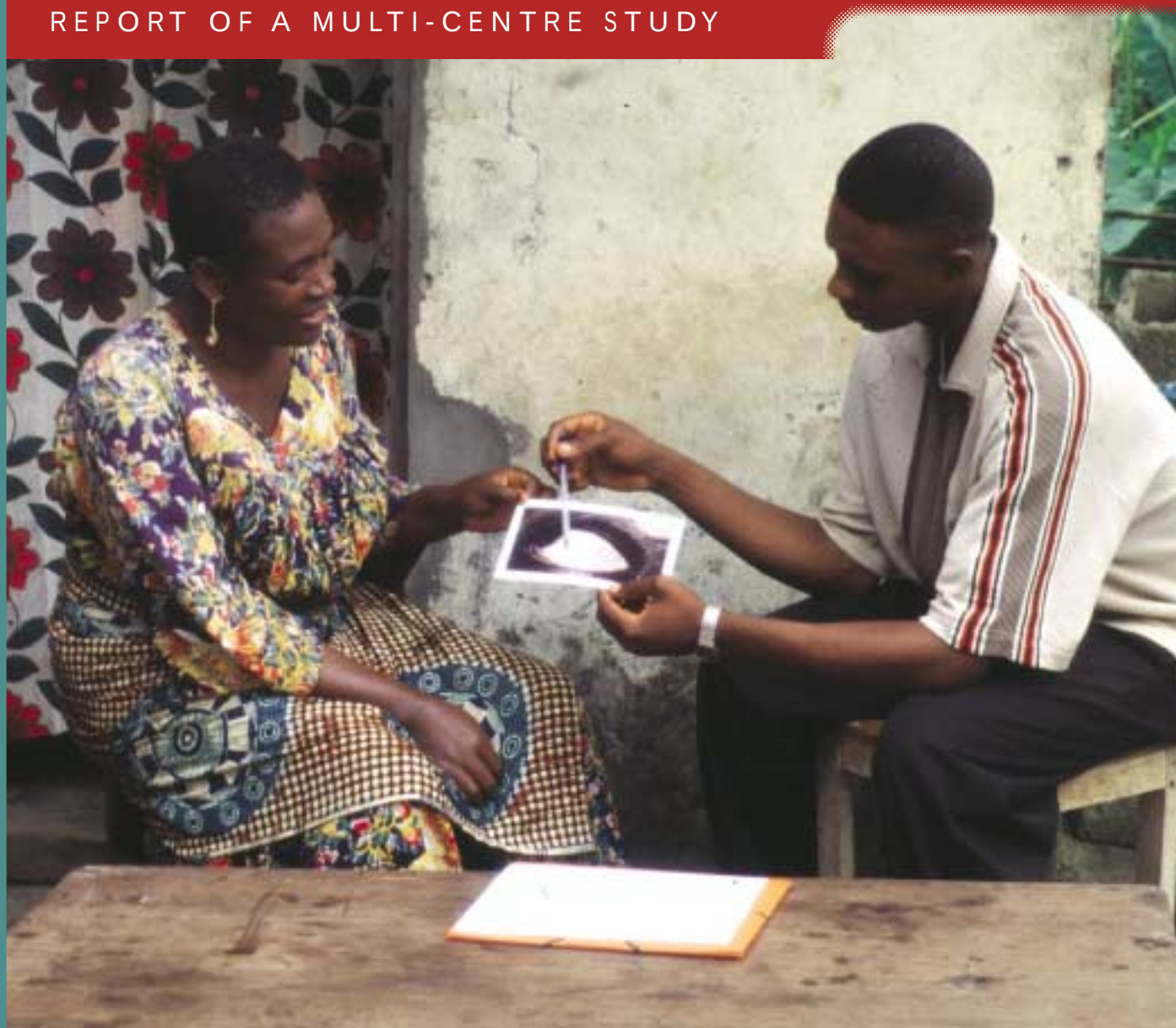
REPORT OF A MULTI-CENTRE STUDY



Rapid Assessment Procedures for Loiasis

UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Disease (TDR)

TDR/IDE/RP/RAPL/01.1

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REPORT OF A MULTI-CENTRE STUDY

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UNDP/World Bank/
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Acronyms

APOC
African Programme for Onchocerciasis Control

CDTI
Community Directed Treatment with ivermectin

TDR
UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

RAP
Rapid Assessment Procedures

RAPLOA
Rapid Assessment Procedure for *Loa loa*.

REW
Restricted Definition of Eye Worm

CMFL
Community microfilarial load

SPSS
Statistical Package for the Social Sciences

GIS
Geographical Information System

SAEs
Severe Adverse Effects

mf
Microfilaria

OCP
Onchocerciasis Control Programme in West Africa

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1

EXECUTIVE SUMMARY

Several cases of severe adverse reactions to ivermectin treatment have been reported from Cameroon in individuals with a high intensity of *Loa loa* infection. Concerns about possible severe adverse reactions have paralysed ivermectin treatment programmes for onchocerciasis in areas that are possibly co-endemic for *Loa loa*. There is an urgent need, therefore, for a simple rapid assessment tool of loiasis endemicity that can help identify communities where there is a high risk of severe adverse reactions.

A multi-centre study supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the African Programme for Onchocerciasis Control (APOC) was carried out in Cameroon and Nigeria to evaluate the use of specific clinical symptoms in rapid assessment of the endemicity of loiasis.

Study communities were selected in areas presumed to be hypo-, meso- and hyper-endemic for *Loa loa* from the Cross River State, south eastern Nigeria (28 communities), the South West and North West Provinces of Cameroon (42 communities) and the Eastern Province of Cameroon (32 communities).

Standardised questionnaires were developed based on key clinical manifestations of loiasis (Eye Worm and Calabar Swelling) and administered by trained interviewers. Eligible individuals had been resident in the community for at least 5 years, were above 15 years of age and had not taken any anti-filarial drug recently. Blood samples were also collected from each individual interviewed and the microfilaraemia determined using the thick blood film method.

The study showed that the clinical manifestations of loiasis were well known in highly endemic communities where local names were associated with them. However, in hypo-endemic communities these local names were not known.

There was a clear relationship between the prevalence and the intensity of *Loa loa* infection. A prevalence of microfilaraemia of 20% corresponded with a prevalence of high loads (> 8,000 mf/ml) of 5% and a prevalence of very high loads (>30,000 mf/ml) of 2%.

Several rapid assessment procedures (RAP), using different combinations of history of Eye Worm and Calabar Swelling, were tested. All RAPs showed a statistically significant correlation with the prevalence and intensity of *Loa loa* infection.

The best results were obtained with RAPLOA, i.e. the percentage of interviewees that reported a history of Eye Worm (defined as a past experience of Eye Worm, confirmed after being shown a photograph of an adult worm in the white part of the eye and with the duration of the most recent episode being between 1-7 days). Using a threshold of 40%, RAPLOA had a sensitivity of 100% and a specificity of more than 90% in identifying high-risk communities.

On the basis of these results, it is recommended that RAPLOA be used to predict the prevalence and intensity of *Loa loa* infection at the community level and the risk of severe adverse reactions after ivermectin treatment.

2

BACKGROUND

Loa loa filaria are found in the rain forest of West and Central Africa where distribution closely parallels that of its vectors *Chrysops silacea* and *Chrysops dimidiata* (Fain, 1981). The common clinical signs of loiasis are the subconjunctival migration of the adult worm (reported for the first time by Mongin in 1770), Calabar Swelling, pruritis, oedemas and arthralgia.

Interest in this filarial species, which has long been considered to be less pathogenic than related species (Pinder, 1988) came from several reports in Cameroon that high microfilaraemia of *Loa loa* is associated with severe and sometimes fatal encephalopathic reactions in patients who had taken ivermectin against onchocerciasis (Poitevin, 1996; Chippaux *et al*., 1996; Gardon *et al*., 1997; Boussinesq *et al*., 1998). The risk of severe adverse reactions is now a major concern for ivermectin treatment programmes in areas that are potentially endemic for *Loa loa* and several treatment programmes for onchocerciasis have come to a standstill.

The risk of severe adverse reactions to ivermectin treatment in *L. loa* infected individuals is related to the intensity of loiasis infection: the risk of developing marked or serious reactions is significantly higher when the *L. loa* load exceeds 8,000 microfilariae/ml, the severity of adverse reactions becomes obvious in patients with more than 30,000 microfilariae/ml and the risk is very high for loads above 50,000 microfilariae/mL (Chippaux *et al*., 1996; Gardon *et al*., 1997). It is critical, therefore, that ivermectin treatment programmes ensure that individuals with such high intensities of *L. loa* infection are not treated or that special provisions are made to ensure that severe adverse reactions are quickly detected and properly managed.

It is not feasible to determine the intensity of loiasis infection for all individuals living in all areas targeted for ivermectin treatment and that are potentially endemic for *Loa loa*. However, if highly infected individuals live in highly endemic communities, the problem would simplify to identifying such communities.

The classical method that has been used routinely to determine the prevalence and intensity of *L. loa* infection at both the individual and community levels is examination under microscope of standardised blood smears. The drawback of this method is that it is time-consuming and cannot be easily applied over the large areas of West and Central Africa where *Onchocerca volvulus* and *L. loa* co-exist and where information on the prevalence and intensity of loiasis is lacking.

A model, using satellite mapping of key environmental factors that determine the development of *Chrysops spp* vectors has been proposed by Thomson *et al.*(2000). This model, which is still undergoing further development, may prove very useful for identifying potential high-risk areas. But there will still be a need for a rapid assessment method for *Loa loa* endemicity at the community level.

Kershaw (1950) and Noireaux *et al.* (1990) suggested the usefulness of specific clinical manifestations (Eye Worm and Calabar Swelling) to assess *Loa loa* at the individual and community level respectively, but this has never been properly evaluated as a rapid assessment tool for loiasis.

The present study was designed to study this question using a carefully designed, standardized methodology and involving a large sample of communities covering a wide range of *Loa loa* endemicity and different ethnic groups.

3
OBJECTIVES

General objectives

The main objective of the study was to develop a Rapid Assessment Procedure (RAP) based on clinical signs of loiasis (history of Eye Worm or Calabar Swelling) which can effectively be used to delineate communities at risk of adverse reactions to ivermectin treatment (i.e. communities with a *Loa loa* prevalence >20%, or more than 5% of individuals with high intensity (>8,000 mf/ml) or more than 2% of individuals with very high intensity (>30,000 mf/ml).

Specific objectives

The specific objectives were:

a) To further refine (and test geographically) the relationship between the prevalence and intensity of *Loa loa* infection.

b) To study the relationship between parasitological indices and the indices based on the clinical manifestations of loiasis.

c) To determine the best rapid assessment index that can be used to assess the level of endemicity of loiasis and risk of severe adverse reactions following ivermectin treatment.

4
METHODOLOGY

Study design

The study was carried out by three research groups based in Buea and Yaounde in Cameroon and in Calabar in Nigeria. Investigations were carried out between April and June 2001. Preliminary field trips were made between April and May 2001. Field data collection took place from May to June 2001. Processing and microscopic analysis of thick blood films were carried out between July and August 2001. The study covered different bio-geographical areas (forest, mosaic forest savannah, savannah and grassland), spreading from low-to highly-endemic regions. Three study sites were chosen with each being investigated by a different research team. Each team was made up of a Principal Investigator, a Parasitologist and a Social Scientist. Two workshops were organised, the first in Mbalmayo, Cameroon to develop a common methodology to be used by all the research teams; and the second in Douala, Cameroon to analyse data collected from the three study sites.

Workshop to standardise methodology

A workshop involving all participating research teams was organised in Mbalmayo, Cameroon in December 2000. During this workshop, individual and community level questionnaires were developed based on specific clinical manifestations of loaisis (the Eye Worm and Calabar Swelling). The parasitological method (thick blood film) to be used in the study was also standardised. Following this workshop, each team organised a local workshop to train interviewers and laboratory technicians.

Pre-testing of methodology

The methodology adopted during the Mbalmayo workshop was pre-tested by all the teams. During pre-testing, members of research teams had opportunities to learn how to work in a co-ordinated manner and acquire knowledge on the preparation of the field trip. It was also an exercise for the interviewers and technicians to be acquainted with the methodology. During the pre-testing, difficulties in the execution of the protocol were observed and amendments were made.

Community questionnaire

A community questionnaire with questions related to the knowledge of Eye Worm, Calabar Swelling and local names associated with theses conditions was used (see appendix 2).

For the Eye Worm, the first question was:

- "Do you know anybody in this locality who reported that sometimes worms move along the white part of the eye?"

If the answer was positive, this was followed by the second question:

- "What is the local name for this condition?"

For the Calabar Swelling, the following two questions were asked.

- "Do you know anybody in this locality who reported swellings under the skin that change position or disappear?"
- "What is the local name for this condition?"

Individual questionnaire

This questionnaire was designed to elicit responses regarding experience of Eye Worm and Calabar Swelling.

For the Eye Worm, the questions related to recent experience of Eye Worm confirmed by a black and white photograph clearly showing a *Loa loa* adult worm in the eye.

The questions were stated as follows:

- "Have you ever experienced or noticed worms move along the white part of your eye?"

After writing down the response, the interviewer then showed a photograph, guided the respondent to recognise the worm in the eye, and asked the second question:

- "Have you ever had the condition in this picture?"

The respondent was then asked a third question:

- "How long (in days) did the worm stay before disappearing?"

For the Calabar Swelling, the questions were related to the transient nature of the swellings and the tendency to itch. The three questions were the following:

- "Have you ever experienced swellings under the skin that change position or disappear (local name for Calabar Swelling)?"
- "How long (in days) did the swelling last before disappearing?" and:
- "Did the swelling itch?"

Administration of questionnaires

The questionnaires were administered by interviewers. Interviews were conducted in English or Pidgin for the Buea and Calabar study teams and in French for the Yaounde study team. Where required, interpreters from the community assisted in the interview process.

For the community questionnaire, village leaders were briefed on the objectives and expected outcomes of the study. The local names of Eye Worm and Calabar Swelling were assessed using key informants. These included village heads, school teachers, health workers, patent medicine dealers, traditional healers, women, group leaders.

For individual questionnaires, households were selected randomly by spinning a bottle at the centre of the village and going in the direction pointed by the mouth of the bottle. Households were each given a sequential study number. In each household, all persons aged 15 years and above and resident in the village for at least 5 years who consented to participate, were included in the study. Interviews of eligible persons in each household were conducted after explaining the objective of the study and obtaining informed consent. In the interview process local names were used to ascertain understanding. Each eligible individual was assigned a code number, interviewed, and a blood sample obtained for parasitological analysis.

Parasitological Methods

Blood collection and processing

After informed consent, each individual interviewed underwent a parasitological examination. A thick blood film was prepared from a standardised 50 µl finger prick blood collected between 10-16:00 hours using a 75 µl non-heparinised capillary tube. A smear was prepared by spreading the blood on a clean slide on an area of 1.5 x 2.5 cm. Each slide was labelled with the code of the individual from whom the blood was collected. The smear was then allowed to dried under shade.

In the laboratory, the blood smears were de-haemoglobinised using tap water for 5-10 minutes and fixed with methanol for 1 minute. They were then stained in 10% Giemsa for 45 minutes and allowed to dry.

Parasite identification

In the study areas, *Mansonella perstans* another species of filariae with blood-dwelling micro-filariae is co-endemic with *Loa loa*. These two parasites were distinguished using microfilarial identification keys (Orihel *et al.* 1997).

Slide reading and expression of results

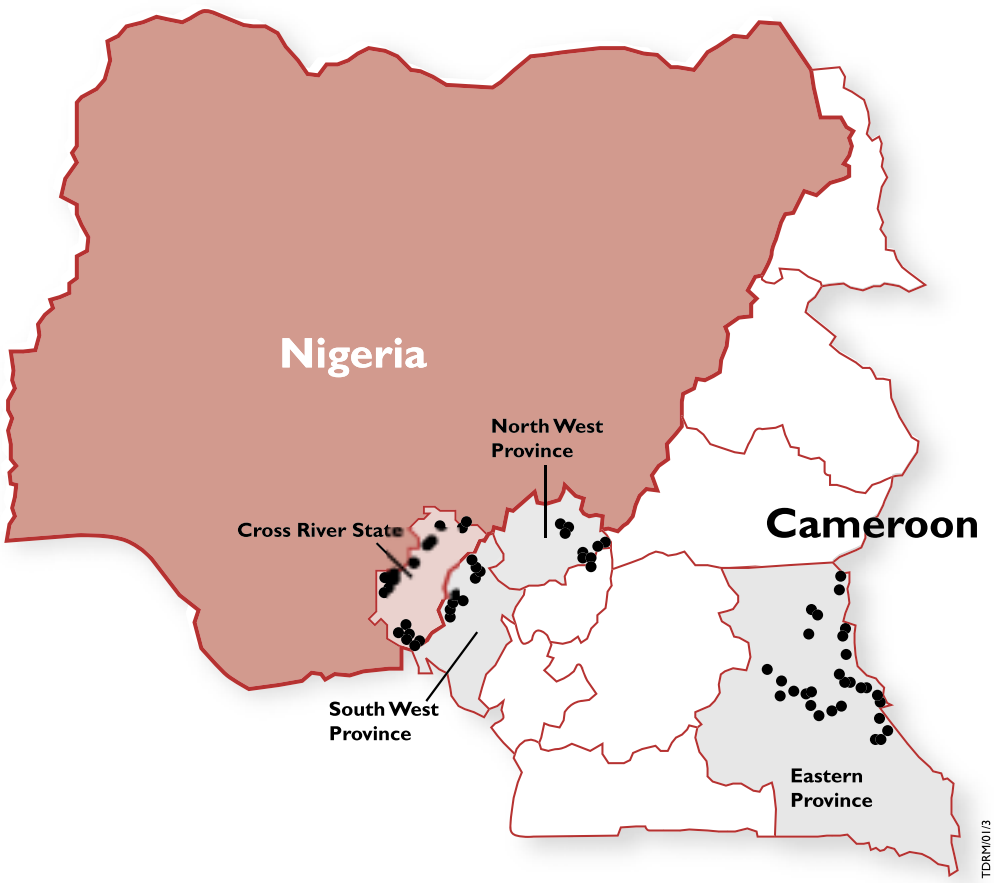
Slides were read by trained technicians under a microscope at x10 maginfication *Loa loa* microfilariae were identified and counted. The counts expressed as microfilariae per millilitre (mf/ml) of blood were recorded on the parasitological record sheet (see Appendix 3).

5
STUDY SITES

Selection of villages

The study involved 102 villages, 28 located in the Cross River State in south-eastern Nigeria, and 74 in Cameroon. Cameroonian villages were situated in the South West (16), North West (26) and in the Eastern Provinces (32). Study villages were selected from areas presumed to be hyper/meso-endemic, hypo-endemic or non-endemic for *Loa loa* based on preliminary field assessment and ecological variations.Villages that were under mass ivermectin treatment were excluded. A collective consent for participation was obtained in each participating village.

Figure 1: Location of study villages



The South West Province of Cameroon

Villages here fall in two bio-geographical zones located in the Manyu Division, the Ejagam and the Takamanda council forest reserves.

The Ejagam Council forest reserve

Situated between altitudes 100 m and 500 m above sea level. Communities selected here lie between latitude 5° N 10' - 5° N 40' and between longitude 8° E 50' - 9° E 10'.
The vegetation is that of the dense evergreen humid rain forest which remains mostly inaccessible and with low population density. The climate is tropical, characterised by the existence of only two seasons, one wet season of about 8 months, and a short dry season. The annual rainfall is above 4,000 mm. The rivers in this forest are tributaries of the Cross River that flows to Nigeria.
The area is sparsely populated, with a density below 20 inhabitants/km^2, and is made up mainly of the Ejagams (97.8 %). Their main occupations are farming and hunting.

The Takamanda Council reserve

Situated between altitudes 100 m and 400 m above sea level. Communities selected here lie between latitude 5° N 50' - 6° N 30' and between longitude 9° E 10' - 9° E 30'. The vegetation is made up of a less dense humid deciduous rain forest with a grassy undergrowth. This forest opens to a tree savannah in its northern part. The climate is tropical with an annual rain fall above 3000 mm. The rivers in this forest are tributaries of the river Manyu that flows into the Cross River.
As in the Ejagam council forest reserve, the area is sparsely populated with population densities below 20 inhabitants/km^2, made up mainly of the Anyangs. People here live from farming, hunting, fishing and trading.

North West Province of Cameroon

Communities were selected from three bio-ecological zones: The Ntem valley (forested or tree savannah), the Misaje area (mosaic forest savannah), and the Mbiame area (highland or grassland), Neba, (1999).

Ntem valley (Mbaw plain)

This area is a plain which lies between altitudes 765 m and 786 m above sea level, between latitudes 6° N 30' - 6° N 40' and longitude 10° E 50' -10° E 40'. The vegetation is made up mainly of the Sudan savannah which is wooded savannah (tree savannah). The vegetation here has been partially altered due to agricultural activities. The climate is the tropical type. The annual rainfall is between 2000 - 4000 mm. The rivers in this area are tributaries of the river Mbam that flows into River Sanaga. The population density is above 60 inhabitants/km^2, and is made up of the Yamba (45.3%) and the Tikari (29.40 %) with the remaining 25.3% being comprised of the Wimbum, Mambella, Banso, Lus, Winson, Nwahwa, Fulani and Ngomko. Their main occupations are farming, hunting and fishing.

Mbiame area (Highland/grassland)

Villages selected in this area lie between altitude 1500 - 2200 m above sea level and between latitude 6° N - 6° N 15', and longitude 10° E 45' - 11° E. The vegetation is made up mainly of the Sudan savannah characterised by grassland and a few shrubs which serves as cropland and

pasture. It has been greatly modified by human activities. The climate is tropical with a rainy season of about 6 months. The annual rainfall is between 1500 - 3000 mm. Rivers are scarce in this area but there are few springs which serve as sources of drinking water.
The population density is above 60 inhabitants/km^2, and is made up of the Banso (71.6 %), Bessah (16.2 %), the Tikari (7.6 %) and the Fulani (3.8 %).

The Misaje area (Mosaic forest savannah)

Villages in this area lie between altitudes 914 - 1100 m above sea level, between latitudes 6° N 30' - 6° N 40' and longitudes 10° E 30' - 10° E 40'. The vegetation is made up mainly of a mosaic forest savannah that serves as cropland/woodland and pasture for cattle. As in the Mbiame area, the vegetation here has undergone a great degradation due to agricultural activities. The climate is tropical but with a rainy season of about 6 months. The annual rainfall is between 2000 - 3000 mm. A few rivers found in this area are tributaries of the river Katsina-ala which flows to Nigeria. The population density is above 60 inhabitants/km^2, and is made up of the Chaney (45 %), the Bessah (23.2 %), the Fulani (10. 5%), Nchanti (10.8%), Banso (4,3%), Banoum (1.8%), Tikari (1.02%) and the remaining 3% made up Haussa, Widikum und Wimbum. Farming and cattle rearing are their main activities.

Eastern Province of Cameroon

Study villages extend between latitude 2° N - 6° N and longitude 13° E - 16° E. The altitude of villages ranges from 650 - 850 m above sea level. The southern part of the study site is situated in the rain forest zone, meanwhile the northern part is situated in the savannah area. The climate is of the Guinean type with annual precipitation ranging from 1500 - 2000 mm. There are four seasons (two rainy seasons and two dry seasons). Main rivers found in the area are Doumé, Sangha, Boumba and Kadei. They flow slowly down the valleys, giving the impression of stagnant water. Marshes constitute ideal breading places for *Chrysops spp*. The Eastern Province has a very low population density (6-12 inhabitant per km^2). The most important ethnic groups are Kako, Gbaya, Foulbe, Bangantou and Mezime. Farming, hunting and cattle rearing are their main activities.

Cross River State, Nigeria

Selected villages of the Cross River state lie between latitude 4° N - 7° N and longitude 8° E - 9° E. The region is characterised by two main seasons, the rainy season lasting from April to October and the dry season which last from November to March. The rainfall is between 1500 - 3000 mm. The vegetation changes from tropical rain forest in the south to Guinea savannah in the north.
The Cross River state has a high population density. The major ethnic groups are Efik, Bette, Eko and Biase. Their main activities are farming and fishing.

6
DATA ANALYSIS

Workshop on data analysis

A workshop was organised in Douala, Cameroon in September 2001 during which data from different research teams were pooled and analysed using the Statistical Package for the Social Sciences (SPSS 10.0). Prevalences of loaisis based on questionnaires and parasitological methods were determined and the relationships between the prevalences from questionnaires and parasitological methods were sought.

Rapid assessment indices

The rapid assessment indices were all based on clinical signs. The percentage of interviewees with a positive history for each of the clinical indicators defined below was calculated in all the communities.

Simple definition of Eye Worm and Calabar Swelling

- Proportion of interviewees with any past experience of Eye Worm
- Proportion of interviewees with any past experience of Calabar Swelling.

Restricted Definition of Eye Worm and Calabar Swelling

- Proportion of interviewees with any past experience of the Restricted Definition of Eye Worm (REW), i.e. history of Eye Worm confirmed with the photograph and which lasted 1-7 days.
- Proportion of interviewees with any past experience of the Restricted Definition of Calabar Swelling (RCS), i.e. any past experience of Calabar Swelling that lasted 1-7 days and itched.

Combined RAP indices

- Proportion of interviewees with history of Restricted Definition of Eye Worm or a history of Restricted Definition of Calabar Swelling (REW or RCS).
- Proportion of interviewees with history of Restricted Definition of Eye Worm and a history of Restricted Definition of Calabar Swelling (REW and RCS).

Parasitological indices

The following parasitological indicators were estimated in all the communities:

- Prevalence of microfilaraemia;
- Prevalence of high microfilarial load > 8,000 mf/ml;
- Prevalence of very high microfilarial load >30,000 mf/ml;

- The Community Microfilarial Load (CMFL) (Geometric mean number of mf/ml in individuals >15 years of age, including mf negatives; see Remme *et al.* 1986).

Relationship between parasitological and/or RAP indices

The following relationships were tested:

- Prevalence based on thick smear and intensity of infection;
- Parasitological and RAP indices using linear regression analysis.

Sensitivity and specificity

The sensitivity, specificity, positive and negative predictive values of all the rapid assessment indices as predictors of high risk communities (prevalence of of *L. loa* mf >20%; prevalence of high mf loads >5% or prevalence of very high mf loads >2%) were computed.

7
RESULTS

Study population

A total of 102 villages were surveyed in the three study sites combined and 12,895 people interviewed and examined. The average age of those examined was 36.5 years and 55% were female.

Table1: Number of communities surveyed and number of individuals interviewed and examined

Study site	No. of villages surveyed	No. of people interviewed and examined
SW/NW Provinces, Cameroon	42	4,532
Eastern Province, Cameroon	32	4,146
Cross River State, Nigeria	28	4,217
TOTAL	**102**	**12,895**

Local names for Eye Worm and Calabar Swelling

The majority of the language groups in the Cameroon study sites had local names for both Eye Worm and Calabar Swelling. All localities visited by the Yaounde study team reported local terms for the two. Terminology for Eye Worm used by the Baya was descriptive of the appearance of the worm in eye. For example 'Pengli' means worm (peng) of the eye (li). A few communities used the term "the filère", a deformation of the French word "Filaire". The remaining ethnic groups had non-descriptive terminology.

To the contrary, only 33 of the localities visited by the Buea team indicated the existence of local terms for the Eye Worm while local terms for Calabar Swelling were reported in only 32 of the villages visited. It is worth noting that in seven of these villages no local terms were identified for either Eye Worm or Calabar Swelling. Five of these villages were lamnso speaking (Dzeng, Kifem, Lam, Rifem, Tanyar) while two were Nchaney speaking (Bem, Mbessa), all situated in highland savannah. The latter were observed to be areas of low endemicity. There were also descriptive terms for the Eye Worm, for instance "Damolenyi" means worm (Damole) of the eye (nyi).

The majority of the localities visited by the Calabar study team had local terms for both the Eye Worm and Calabar Swelling. Some of the terms did not exclusively describe the condition particularly in very low-endemic areas.

The most commonly cited location for the Calabar Swelling was the hand, arm and leg in order of importance. But there were also references to the whole body and Calabar Swelling appeared less specific for the perception of *Loa loa* than Eye Worm.

A list of the language groups and local terms collected with the community-level questionnaire are presented in table 2.

Table 2: Language groups and local terms for Eye Worm

Site	Language Group	Local Terms	Number of Villages
North West/ South West Provinces, Cameroon	Ejagam	Esongoeyet	9
	Denya	Damolenyi	7
	Salli	Fintsong	2
	Nchaney	Ngulih	3
		Nnuilih	1
		Not Available	2
	Yamba	Nnuilih	4
	Lamnso	Not available	7
	Tikari	Nteh	4
		Nnuilih	1
	Mbohmboh	Nnuilih	1
	Multilingual (Lip, Mbiripkwa)	Nteh (Tikar term)	2
	Nngunawah	Nnuilih	1
East Province, Cameroon	Baya	Yolo li	7
		Peng li	3
	Foulbe	Guilde guite	10
	Kako	Kon missi	11
		Ntoro	1
	Maka	Da biep naki	2
	Mbimou	Ntoli	1
	Pol	Kon mich	2
	Mezime	Djol	2
	Bangantou	Djol	2
	Mvongvom	Dol	1
Cross River State, Nigeria	Efik	Etung Enyin	13
		Uhira	1
	Biase	Iraboni Egen	2
	Bahumono	Butum	1
		Izanga	1
	Yakurr	Liyon	1
	Mbembe	Not Available	2
	Bette	Unyangutungshi	4
		Ugi-Utorshi	1
	Nkim	Not Available	1
	Bakor	Not Available	1

The following deductions can be made from the table:

- Some local names cut across language groups which are situated within the same bio-geographical zones and which have more or less the same level of endemicity.

- Language groups falling in areas of low endemicity generally did not have local names.

- Some language groups had more than one name depending on the nature of the spread of the community. For example the Baya group is divided into several segments and spread over a large area with different segments speaking different dialects as their various neighbours influence them. It is therefore not surprising to find the same Baya having two terms for the same condition of Eye Worm.

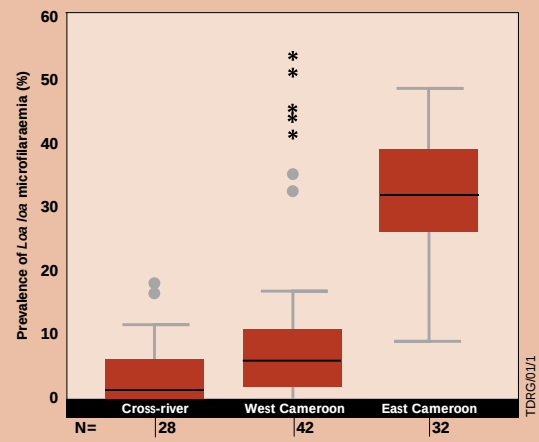
- In multilingual areas, in the East Province of Cameroon, more than one term for Eye Worm was sometimes used within the same villages.

Prevalence and intensity of *Loa loa* infection

Prevalence of *Loa loa* infection

The overall prevalence of microfilaraemia varied considerably between study sites (Figure 2). The Cross River State in Nigeria had the lowest prevalence, ranging from 0 - 17%, with a median prevalence of only 1.5%. In East Cameroon, the prevalence of microfilaraemia was much higher, ranging from 8 - 47% with a median prevalence as high as 31%. The South West/North West Provinces of Cameroon showed the widest range of endemicity: most villages had a prevalence of less than 10% (median 8%) but there were 7 villages with very high prevalence, including the village with the highest microfilaraemia prevalence of all (53%).

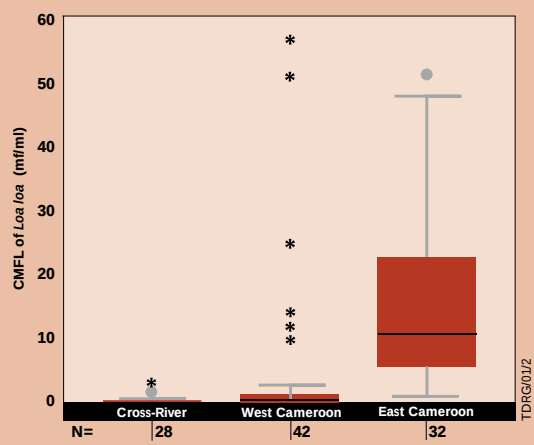
Figure 2: Prevalence of *L. loa* infection in different study sites



Intensity of *Loa loa* infection

The difference between the study sites was even more striking for the community level of intensity of *Loa loa* infection, as measured by the Community Microfilarial Load (CMFL). In all villages in Cross River State in Nigeria, the CMFL was close to zero, while the median CMFL in East Cameroon was greater than 30 mf/ml (Figure 3). Again, the pattern in SW/NW Provinces of Cameroon covered the widest range with most communities having a low intensity of infection but some having the highest CMFL.

Figure 3: Intensity of *L. loa* infection in different study sites



Relationship between prevalence and intensity of loiasis

Figure 4 shows the prevalence of high intensity of *L. loa* infection (> 8,000 mf/ml) in relation to the preva-

Figure 4: Relationship between prevalence of high intensity of *L. loa* infection and prevalence of microfilaraemia

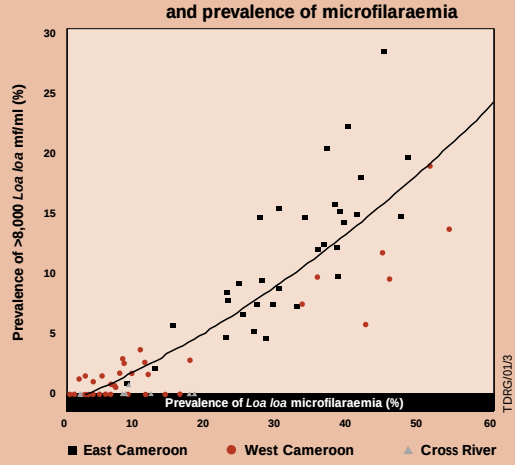


Figure 5: Relationship between prevalence of very high intensity of *L. loa* infection and prevalence of microfilaraemia

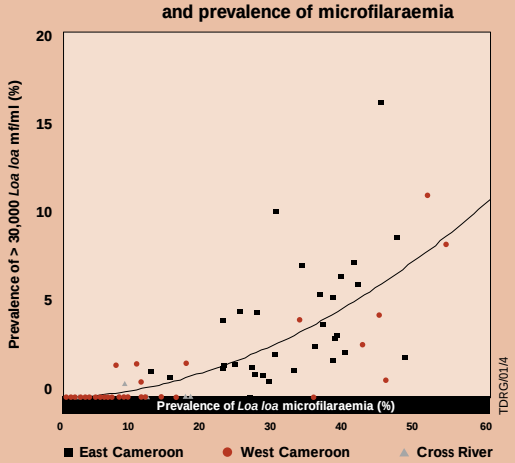
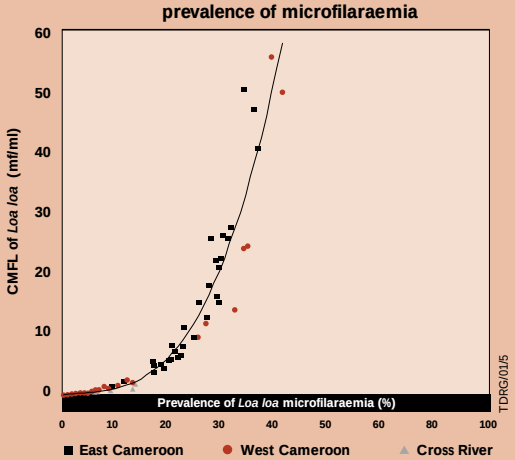


Figure 6: Relationship between Community Microfilarial Load of *L. loa* and prevalence of microfilaraemia



lence of *L. loa* microfilaraemia. The percentage of people with a high mf load of more than 8,000 mf/ml increases with an increase in *L. loa* prevalence, and there exists a very clear relationship between the two indices (Spearman rank correlation coefficient of 0.865, P<0.01). The pattern is similar for East and West Cameroon, and the results for Cross River State also fit in the overall pattern. These results are nearly identical to those reported by Boussinesq *et al.* (2001) for the Central Province of Cameroon.

The prevalence of very high loads of *L. loa* microfilariae (>30,000 mf/ml) in relation to the overall prevalence of *L. Loa* is given in Figure 5. Again, there is a clear relationship between the two indices (Correlation coefficient 0.818, P<0.01) and the relationship is also very similar to that reported for Central Cameroon. Hence, it can be safely assumed that the intensity and prevalence of *L. loa* infection are directly related, and that the risk of high intensity of infection increases with prevalence of infection. The results are also consistent with the conclusion of Boussinesq *et al.* (2001) that a 20% prevalence of *L. loa* microfilaraemia corresponds to a 5% prevalence of high microfilarial loads (>8,000 mf/ml) and to a 2% prevalence of very high microfilarial loads (>30,000 mf/ml).

The relationship between CMFL and prevalence of microfilaraemia is presented in Figure 6. The CMFL rises with an increase in the prevalence, initially slowly but the increase accelerates rapidly from a prevalence of 20% onwards. The relationship between CMFL and prevalence appears to have a hyperbolic shape, suggesting an upper limit of the prevalence of microfilaraemia at around 60%. It has been previously observed that a significant proportion of the population in a *L. loa* endemic community may be symptomatic but amicrofilaraemic, probably because they are able to mount an efficient immune response (Pinder, 1988; Noireau *et al.* 1990; Garcia *et al.* 1999). It is worth noting the ten-fold increase in CMFL over the rather short prevalence range between 30 - 50%. This dramatic increase in CMFL suggests major increases in adult worm loads, possibly related to significant increase in intensity of transmission, in spite of the limited variation in prevalence of patent infection.

Table 3: Spearman correlation coefficients for correlation between Rapid Assessment Indicators and Parasitological Indicators of* L. loa *endemicity

Rapid Assessment Indicator	Parasitological indicator of *Loa loa endemicity*			
	Prevalence of micro-filaraemia	Prevalence of >8,000 mf/ml	Prevalence of >30,000 mf/ml	CMFL
% with history of Eye Worm	0.782 **	0.753 **	0.793 **	0.778 **
% with history of Restricted Definition of Eye Worm (REW)	0.850 **	0.812 **	0.813 **	0.855 **
% with history of Calabar Swelling	0.748 **	0.698 **	0.739 **	0.743 **
% with history of Restricted Definition of Calabar Swelling (RCS)	0.693 **	0.651 **	0.709 **	0.683 **
% with REW or RCS	0.799 **	0.755 **	0.786 **	0.795 **
% with REW and RCS	0.812 **	0.768 **	0.781 **	0.811 **

** : P<0.01

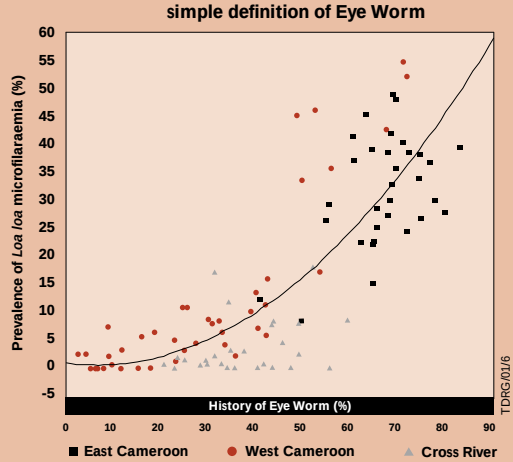
Relationship between parasitological and RAP indices

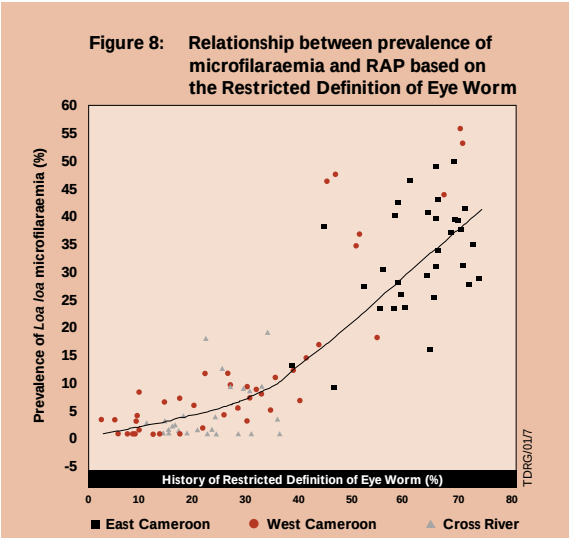
The main purpose of the study was to determine whether the rapid assessment methods can be used to predict the level of *L. loa endemicity* at the community level. In this section, we show the relationship between the rapid assessment indices and the parasitological indices for the 102 study villages. Table 3 shows the Spearman correlation coefficients for the relationship between the 6 RAP indices and the 4 parasitological indices. All the RAP indices showed a statistically significant relationship with the parasitological indices. There was a better correlation for RAP indices based on Eye Worm than those based on Calabar Swelling. The highest correlation coefficients were obtained with the Restricted Definition of Eye Worm (i.e. history of Eye Worm + confirmation by photograph + reported duration less than 7 days). The correlation coefficients for RAP indices that combined Eye Worm and Calabar Swelling were lower than the correlation coefficients for the Restricted Definition of Eye Worm alone.

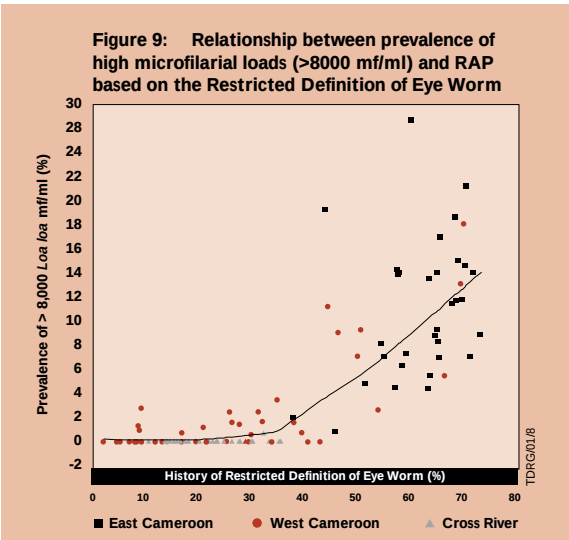
Simple definition of the Eye Worm

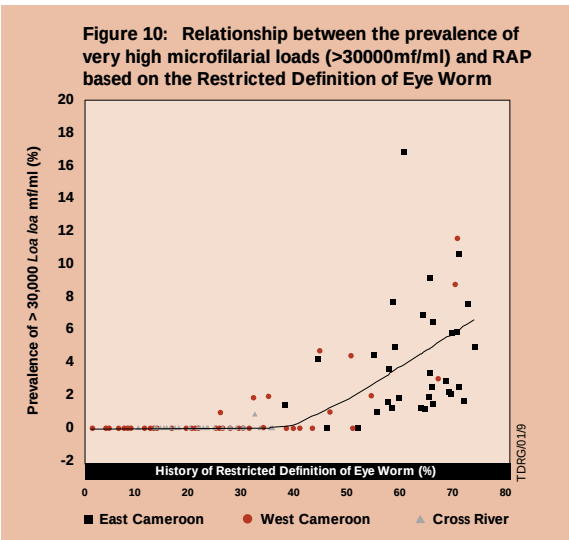
The relationship between the RAP index based on the simple definition for the Eye Worm (i.e. reported history of Eye Worm irrespective of confirmation by photograph or by reported duration of experience) and the prevalence of microfilaraemia is shown in Figure 7. There is a clear relationship between the two indices and the pattern for East and West Cameroon is similar. However, in the Cross River area (characterised by low *L. loa* endemicity), relatively high prevalences of

Figure 7: Relationship between prevalence of microfilaraemia and RAP based on simple definition of Eye Worm









Eye Worm were reported for low prevalences of microfilaraemia. This would seem to confirm that in areas of low endemicity, the simple question on the issue of the Eye Worm may not be sufficiently specific.

Restricted Definition of the Eye Worm

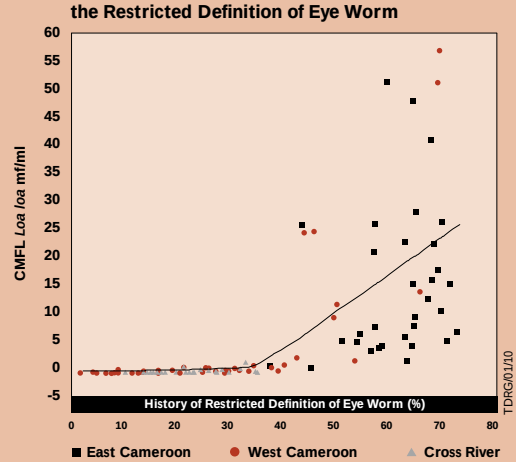
The relationship for the Restricted Definition of Eye Worm is shown in Figure 8 The results for Cross River State are now similar to those for the other sites. Hence, using the Restricted Definition of Eye Worm has improved on the specificity of the rapid assessment and it is for this reason that we recommend the use of the restricted instead of the simple definition of Eye Worm. The Restricted Definition of Eye Worm can be used to predict the level of *endemicity of L. loa*, and a prevalence of microfilaraemia of 20% corresponds with some 40% of those interviewed reporting a history of Eye Worm. Hence, we propose a threshold of 40% for the percentage of interviewees reporting a history of the restricted definition of Eye Worm, above which communities should be considered at risk of severe adverse reactions after ivermectin treatment.

The relationship between the prevalence of high mf loads (>8,000 mf/ml) and the RAP based on the restricted definition of Eye Worm is shown in Figure 9. There is a clear, non-linear relationship and the prevalence of high loads rises sharply when more than 40% of interviewees report a history of the Restricted Definition of Eye Worm. Below the 40% threshold, high microfilarial loads of >8,000 mf/ml are relatively rare. The prevalence of high loads is < 5% for all communities below the 40% RAP threshold, and >5% for nearly all communities above the 40% threshold.

The relationship between the prevalence of very high microfilarial loads (>30,000 mf/ml) and the RAP based on the Restricted Definition of Eye Worm is given in Figure 10. Again, the threshold of 40% provides a good division between high and low risk communities. Above the threshold the prevalence of very high microfilarial loads increases rapidly but below the 40% threshold very high microfilarial loads were rare and even completely absent if less than 25% of respondents reported a history of Eye Worm.

The discriminating power of the threshold of 40% Eye Worm history becomes even more distinctly clear in Figure 11 which shows the relationship between the CMFL and the RAP based on the Restricted Definition of Eye Worm. All CMFL's are close to zero below the 40% threshold but the CMFL starts rising significantly from the threshold upward.

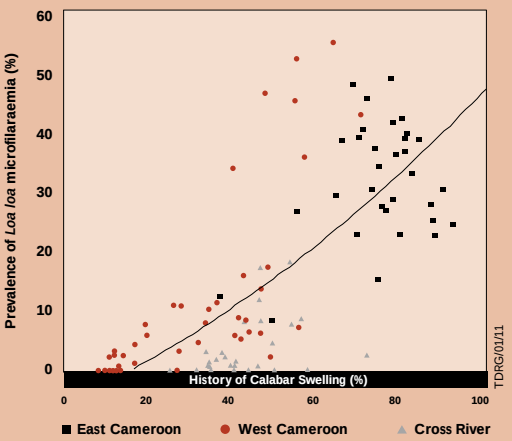
Figure 11: Relationship between Community Microfilarial Load of *L. Loa* and RAP based on the Restricted Definition of Eye Worm



Simple and Restricted Definition of Calabar Swelling

The relationship between the percentage of respondents reporting a history of Calabar Swelling and the prevalence of microfilaraemia is shown in Figure 12. Also the Calabar Swelling shows a relationship with prevalence of *L. loa*, but there is considerable variation between sites. For the same low prevalence of microfilaraemia, many more people report Calabar Swelling in Cross River State than in the NW/SW Provinces of Cameroon. As for the Eye Worm, this probably reflects a tendency of over-reporting in areas where *L. loa* is not common. However, contrary to the Eye Worm, the introduction of a restricted definition of Calabar Swelling did not improve the results very much as can be seen in Figure 13. Even for the Restricted Definition of Calabar Swelling, there were systematic differences for the patterns for Cross River State and NW/SW provinces of Cameroon.

Figure 12: Relationship between the prevalence of *L. loa* microfilaraemia and RAP based on simple definition of Calabar Swelling

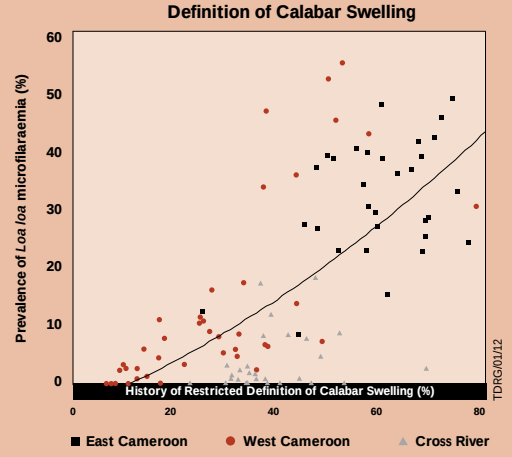


Combined RAP for Calabar Swelling and Eye Worm

When the Restricted Definition of Calabar Swelling and the Restricted Definition of Eye Worm were combined into one RAP index (positive meaning positive to either of the two separate indices), the threshold increased from 40% to 60% (Figure 14). The combined RAP index also performed well. However, there is still a difference in the pattern observed for Eastern Cameroon and Cross River State at low prevalence levels, probably due to the lesser specificity of Calabar Swelling compared to Eye Worm.

The relationship between the prevalence of high microfilarial loads (>8,000 mf/ml) and the RAP

Figure 13: Relationship between the prevalence of *L. loa* microfilaraemia and RAP based on the Restricted Definition of Calabar Swelling



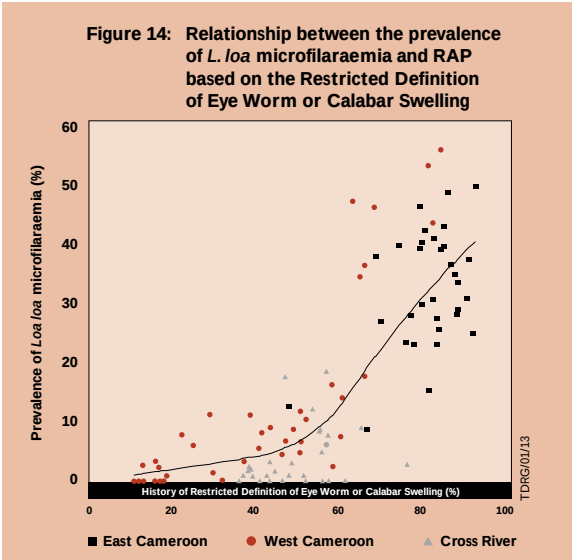


Figure 14: Relationship between the prevalence of *L. loa* microfilaraemia and RAP based on the Restricted Definition of Eye Worm or Calabar Swelling

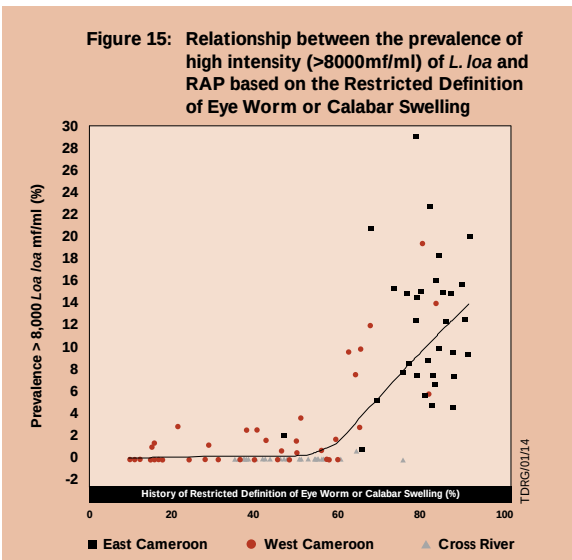


Figure 15: Relationship between the prevalence of high intensity (>8000mf/ml) of *L. loa* and RAP based on the Restricted Definition of Eye Worm or Calabar Swelling

based on the history of Restricted Definition of Eye Worm or Calabar Swelling is given in Figure 15. Prevalence of high microfilarial loads rises sharply when more than 60% of interviewees report a history of Eye Worm and Calabar Swelling. Below 60%, high microfilarial loads of >8,000 mf/ml are relatively rare. The prevalence of high loads is less than 5% for all communities below the 60% RAP threshold and greater than 5% for nearly all communities above the 60% threshold.

Sensitivity and specificity

Using the above graphs, and similar graphs for the other RAP indices studied, thresholds were identified that corresponded with the parasitological thresholds that define high-risk communities (i.e. 20% prevalence of microfilaraemia, 5% prevalence of mf loads >8,000 mf/ml, and 2% prevalence of mf loads >30,000 mf/ml). Using those thresholds, all communities were reclassified as high or low risk. This classification was then compared with the parasitological classification of the same communities to determine the sensitivity and specificity of the RAP methods to identify high-risk communities. The results are shown in Table 4.

All RAPs showed a very good sensitivity (94 - 100 %). The specificity ranged from 48 - 92%. Specificity was relatively low for the simple definitions of Eye Worm and Calabar Swelling. For both the simple and restricted definition the specificity of Eye Worm was much better than that of Calabar Swelling. The best performance was obtained with the Restricted Definition of Eye Worm which had a sensitivity of 100% and a specificity of 79 - 92%. This implies that we can use a RAP based on a simple questionnaire to predict parasitological prevalence and intensities, and thus the risk of possible severe adverse reactions to ivermectin treatment.

Table 4: Sensitivity and specificity of the different RAP's for identifying high-risk communities

RAP	Indicator of high-risk	Sensitivity (%)	Specificity (%)	Pos. pred.Value (%)	Neg. pred Value (%)
History of Eye Worm >40%					
	Prev. *L. loa* >20%	100	66.7	62.1	100
	Prev. more than 8000 mf/ml >5%	100	65.7	60.3	100
	Prev. more than 30000 mf/ml >2%	100	57.1	43.1	100
History of Swelling >40%					
	Prev. *L. loa* >20%	100	56.1	55.4	100
	Prev. more than 8000 mf/ml >5%	100	55.2	53.8	100
	Prev. more than 30000 mf/ml >2%	100	48.1	38.5	100
Eye Worm (Restricted Definition) >40%					
	Prev. *L. loa* >20%	100	92.4	87.8	100
	Prev. more than 8000 mf/ml >5%	100	91.0	85.4	100
	Prev. more than 30000 mf/ml >2%	100	79.2	61.0	100
Calabar Swelling (Restricted Definition) >40%					
	Prev. *L. loa* >20%	94.4	78.8	70.8	96.3
	Prev. more than 8000 mf/ml >5%	94.3	77.6	68.8	96.3
	Prev. more than 30000 mf/ml >2%	96	68.8	50	98.1
Eye Worm (RD) or Calabar Swelling (RD) >60%					
	Prev. *L. loa* >20%	100	89.4	83.7	100
	Prev. more than 8000 mf/ml >5%	100	88.1	81.4	88.1
	Prev. more than 30000 mf/ml >2%	100	76.6	58.1	100
Eye Worm (RD) or Calabar Swelling (RD) >20%					
	Prev. *L. loa* >20%	100	89.4	83.7	100
	Prev. more than 8000 mf/ml >5%	100	88.1	81.4	100
	Prev. more than 30000 mf/ml >2%	100	76.6	58.1	100

8
MAIN CONCLUSIONS

Local names for Eye Worm and Calabar Swelling

All highly-endemic communities had local names for Eye Worm which were widely known to the members of the community. There were also local names for Calabar Swelling, but these were less specific.

Wide range of prevalence and intensity of loiasis amongst study areas

The prevalence and intensity of *L. loa* infection varied considerably between study sites, with the Cross River State in Nigeria having low endemicity, the South West and North West Provinces of Cameroon a wide range of endemicity from low to very high, and the Eastern Province of Cameroon having a very high endemicity.

Relationship between prevalence and intensity of loiasis

There was a clear relationship between the prevalence and the intensity of *L. loa* at the community level confirming the previous finding of Boussinesq *et al.* (2001) in the Central province of Cameroon. There was also a hyperbolic relationship between the CMFL and the prevalence of *L. loa* infection, suggesting an upper limit for prevalence of microfilaraemia around 60 %.

Correlation between parasitological and RAP indices.

All RAP indices showed a statistically significant relationship with the prevalence and intensity of *L. loa*, indicating that RAP indices can be used to predict the prevalence and intensity of *L. loa* infection.

Sensitivity and specificity of RAPs.

The sensitivity of all the six RAP indices was high (94 - 100 %) and the specificity ranged from 48 - 92%.

The best RAP index

RAPs based on the history of Eye Worm performed better than those based on Calabar Swelling. The best rapid assessment index (RAPLOA) was based on the Restricted Definition of Eye Worm, i.e. a history of Eye Worm confirmed by the photograph and the duration of the most recent episode lasting between 1-7 days.

A RAPLOA score of 40 % or more indicates a high risk of adverse reactions during mass treatment with ivermectin. Using a RAPLOA score of 40 % as threshold, the sensitivity of RAPLOA for diagnosing high-risk communities was 100 % and the specificity >90 %.

9
RECOMMENDATION

RAPLOA, the Rapid Assessment Procedure that is based on the Restricted Definition of Eye Worm, should be used for the rapid assessment of community prevalence and intensity of *Loa loa* infection in areas in African countries where large-scale ivermectin treatment of onchocerciasis or lymphatic filariasis is planned and where co-endemicity of loiasis is suspected.

10
ACKNOWLEDGEMENTS

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We are grateful to the residents of the study communities for their co-operation during the surveys.

APPENDIX 1
COMMUNITY QUESTIONNAIRE

COMMUNITY LEVEL QUESTIONNAIRE

State/Province _____ LGA/District _____

Village/Locality_____ Code _____

Has there been any mass distribution of ivermectin ? /__/ Yes /__/ No

Estimated population /__/__/__/__/__/__/

Estimated number of households /__/__/__/__/

Local languages/dialects _____

- Do you know anybody in this locality who reported that sometimes worms move along the white part of the eye (yes / no)
- What is the local name for this condition _____
- Do you know anybody in this locality who reported swellings under the skin that change position or disappear (yes / no)
- What is the local name for this condition _____

APPENDIX 2
INDIVIDUAL QUESTIONNAIRE

INDIVIDUAL RAP QUESTIONNAIRE

Name of interviewer _____

Date of interview _____ Study team /__/

Village Name _____ Village /__/__/

Name Head of Household _____ Household /__/__/

Name of Respondent _____ Individual /__/__/

EXCLUSION CRITERIA

(a) AGE < 15 years

(b) RESIDENCE IN AREA < 5 years

RESPONDENT CHARACTERISTICS

1) Age /__/__/ 2) Sex /__/

3) Ethnic group _____

4) Occupation _____

5) Educational status

/__/ Never been to school

/__/ Primary level

/__/ Secondary level

/__/ Higher level

6) For how long have you been resident in this locality (in years) /__/__/

SIGNS AND SYMPTOMS

7) Have you ever experienced or noticed worms move along the white of your eye?

/__/ Yes

/__/ No

At this moment, show the interviewee a picture of Eye Worm

8) Have you ever had the condition in this picture? /__/ Yes

/__/ No

If No in 7) and 8), go to Question 13

If Yes in either 7) or 8), continue with Question 9

9) How many times have you experienced this over the past one year? /__/__/ times

10) How long ago did you last experience it? /__/__/ months

11) How did you know you had this condition (don't probe)?

/__/ In the mirror

/__/ Somebody told me

/__/ Diagnosed in health facility

/__/ Others (specify) _____

12) How long did the worm stay before disappearing? /__/__/ days

Others (specify) _____

13) Do you know of any person in this locality who had this condition?

/__/ Yes

/__/ No

If yes, who?

- In the same household? (Give sequential study number if adult) _____
- Others in the village? How many /__/__/

14) Have you ever experienced swellings under the skin that change position or disappear (local name for Calabar Swelling)?

/__/ Yes

/__/ No (**If No**, go to Question 20)

15) **If yes** how many times have you experienced this condition over the past one year?

/__/__/ times

16) On what part(s) of your body did the swelling occur?

/__/ Face /__/ Trunk

/__/ Arms /__/ Buttocks

/__/ Hand /__/ Legs

/__/ All over the body /__/ Other (specify) _____

17) For how long did the swelling last? /__/__/ days.

18) Was this particular swelling:

/__/ Very painful

/__/ Slightly painful

/__/ Not painful

19) Did the swelling itch?

/__/ Yes

/__/ No

20) Do you know of any persons in this locality who had this type of swelling?

/__/ Yes

/__/ No

If yes, who?

- In the household? (Give sequential study number if adult) _____
- Others in the village? How many /__/__/

21) Have you ever been treated for Filaria (local term).

/__/ Yes

/__/ No

If yes, when was the last time _____

APPENDIX 3
PARASITOLOGICAL RECORD SHEET

ID Number				Thick Blood Film		
T	VV	HH	II	*L. loa* (mf/50 ml)	*M. perstans* N. (mf/50 ml)	*W. bancrofti* (mf/50ml)

T = Study team;

VV = Village or Community;

HH = Household Number;

II = Individual Number,

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