

## VALIDITY OF NODULE PALPATION IN A *SIMULIUM NEAVEI*-TRANSMITTED ONCHOCERCIASIS AREA IN UGANDA

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**Abstract.** The objective of this study was to evaluate the prevalence of palpable nodules as a rapid indicator for onchocerciasis endemicity in at-risk communities where *Simulium neavei* s.s. is the transmitting vector. We used data collected from 13 villages in Uganda to determine the validity of this rapid assessment method. The prevalence of palpable nodules was closely associated with the microfilarial prevalence ( $R^2 = 0.603$ ,  $P = 0.002$ ), with the community filarial load ( $R^2 = 0.620$ ,  $P = 0.001$ ) and with the prevalence of onchodermatitis. Nodule palpation in males more than 20 years old, using a cut-off point of 40% and higher for the nodule prevalence, had a sensitivity of 92% and a specificity of 100% in correctly identifying communities in need of urgent intervention with ivermectin mass treatment. Cut-off points were based on World Health Organization recommendations. Thus, nodule palpation can replace skin snipping to identify communities at serious risk of *S. neavei*-transmitted onchocerciasis.

### INTRODUCTION

Rapid assessment procedures to determine endemicity of diseases and to facilitate the planning of disease control programs have recently become more important. This is mainly due to the availability of new technologies for mass interventions (e.g., ivermectin tablets for treatment and control of onchocerciasis). The application of drugs to the entire or major part of the population requires the intimate knowledge of disease endemicity levels in specific areas of a country. These levels could be used to determine if mass treatment should be introduced as part of a disease control strategy. The World Health Organization (WHO) has introduced the principal of “Rapid Epidemiological Assessment”<sup>1</sup> and “Methods for Community Diagnosis of Onchocerciasis to Guide Ivermectin Based Control in Africa.”<sup>2</sup>

In onchocerciasis areas, nodule palpation in adult males more than 20 years old can be used to estimate prevalence and endemicity of *Onchocerca volvulus* infection in West Africa. Taylor and others reported in one of the first papers on this topic that nodule prevalence rates could be reliably used as a rapid, non-invasive means of assessing the level of endemicity in a community in relation to the need for treatment with ivermectin.<sup>3</sup> Ngoumou and others used nodule palpation to map endemicity levels in a nationwide exercise in Cameroon. They found a significant correlation between nodule prevalence and prevalence of mf carriers.<sup>4</sup> The mean number of nodules also correlated well with the community microfilarial load (CMFL), based on results from 28 villages in the Onchocerciasis Control Program (OCP) area.<sup>2</sup> In the savanna areas of the OCP, the CMFL showed also a linear relationship with ocular indicators. In Nigeria, nodule palpation was evaluated as a useful way to determine the microfilaria (mf) prevalence in Imo and Bendel States, while in Plateau State it was not found to be useful (because of the missing relationship between nodule prevalence and prevalence of mf carriers), indicating some local variation in the parasite and/or vector.<sup>2</sup>

No information on the validity of nodule palpation as a rapid assessment tool for the community diagnosis of onchocerciasis has been published from parts of Africa where *Simulium neavei* s.l. is the main transmitting vector. The WHO estimates that 6.5 million cases of onchocerciasis exist in areas in eastern and central Africa where *S. neavei* s.l. is

transmitting *O. volvulus*. In Uganda, where *O. volvulus* is predominantly transmitted by *S. neavei* s.s., an estimated 1.2 million people have onchocerciasis.<sup>5</sup> Since delivery of ivermectin has started or will soon start in many of these areas, nodule palpation will be (or is already) the most important rapid assessment tool available at low costs that will facilitate the assessment of the endemicity level of transmission of *O. volvulus*.

We report results from a study carried out in Kigoyera Parish in western Uganda, which is located in an *S. neavei* s.s.-transmitted area of onchocerciasis within the Ruwenzori focus. The objectives of this study were to 1) assess the validity of nodule palpation for estimating the microfilarial prevalence and CMFL in a known endemic region of forest onchocerciasis where *S. neavei* s.s. is the transmitting vector, 2) determine the relationship between the nodule prevalence and the prevalence of onchodermatitis, and 3) calculate sensitivity and specificity of nodule palpation as a tool to correctly identify villages' eligibility for ivermectin mass treatment, using WHO criteria for urgent ivermectin mass treatment programs.

*Simulium neavei* s.s.-transmitted onchocerciasis in the Ruwenzori focus in western Uganda has been characterized to be different from the onchocerciasis observed in the West African rain forest, which is transmitted by *S. damnosum* s.l. and other *Simulium* species. DNA probes ascertained that the *O. volvulus* strain from Uganda differed significantly from *O. volvulus* strains in the forests of Liberia, Ghana, Benin, and Cameroon.<sup>6</sup> In addition, high levels of infection with *O. volvulus* in the Ruwenzori focus were reported in many cases: for example, 25% of the males in Kigoyera Parish had  $\geq 100$  mf per skin snip; and nine of the 13 villages had a CMFL in males  $\geq 60$  mf per skin snip.<sup>7</sup> There are no published data to our knowledge in which such high levels of infection in men with onchocerciasis were reported from West Africa. Comparisons of clinical symptoms also suggested that onchocercarial skin disease was a bigger problem in the Ugandan focus compared with rain forest foci in West Africa.<sup>7</sup>

### MATERIALS AND METHODS

We examined data from our earlier study on onchocerciasis from 13 villages in Kigoyera Parish, which is located in the northern part of Kabarole district (9°52'N, 30°32'E for Kigoy-

TABLE 1  
Onchocerciasis data from 13 villages in Kigoyera Parish, Uganda<sup>7\*</sup>

Name of village	Prevalence of nodules in males >19 years old (%)	Intensity of infection in males, (CMFL, mf/snip)	Prevalence of mf carriers (%)	Prevalence of dermatitis (%)
Kigoyera	42	36	77	20
Kajuma	48	48	74	21
Itwara	53	103	87	27
Byeya	69	110	93	46
Kakira	54	126	89	31
Kibangali	48	39	76	23
Mirambi	50	39	77	20
Katambale	65	76	89	36
Kitembe	60	87	90	28
Igoma A	66	128	93	44
Igoma B	47	68	81	28
Mwokya	37	63	89	21
Kibaale	61	108	91	67

\* CMFL = community microfilarial load; mf = microfilaria.

era village). The design and results of this study are published elsewhere.<sup>7</sup> A total of 3,268 people were examined in the 13 villages. The population in the villages ranged from 305 to 918 inhabitants. The examination included clinical assessment, nodule palpation according to the WHO protocol, and examination of the skin for the presence of mf of *O. volvulus*. Details of the patient examinations procedures have been previously reported (Table 1).

We assessed a possible association between the prevalence of nodules and other important variables in the diagnosis of onchocerciasis such as the prevalence of mf carriers, the CMFL, and the prevalence of onchodermatitis. Statistical analysis was done using linear regression technique. To test for an association between the prevalence of nodule carriers and the prevalence of mf, intensity of infection (CMFL), and prevalence of onchodermatitis, a regression model was applied. The independent variable was the nodule prevalence, while the prevalence of mf carriers and the CMFL were the used as the dependent variable. A similar regression model was developed with the nodule prevalence as the independent variable and the prevalence of onchodermatitis as the dependent variable. This was done separately for males and males plus females. The validity of the model was assessed by examining the distribution of the data and the standard residuals and the plots of the residuals versus the covariate. The Shapiro-Wilk test was used for analysis of a normal distribution of the dependent variable and the standard residuals (Stata 5.0, Stata Corporation, College Station, TX).

Sensitivity of nodule palpation, using prevalence of infection with *O. volvulus* as selection criteria, was calculated as the proportion of high mf-positive villages (cut-off point > 60%) with a prevalence of one or more nodules (cut-off point  $\geq$  40%). Specificity was calculated as the proportion of lower mf prevalence villages less than the cut-off point with a prevalence of one or more nodules (cut off point  $\geq$  40%). Sensitivity of nodule palpation, using the CMFL as the selection criteria, was calculated as the proportion of high CMFL villages (cut-off point > 20 mf/skin snip) with a prevalence of one or more nodules (cut-off point  $\geq$  40%). Specificity was calculated as the proportion of CMFL in villages lower than the cut-off point with a prevalence of one or more nodules (cut-off point  $\geq$  40%). The thresholds or cut-off points were based on WHO recommendations for urgent interventions

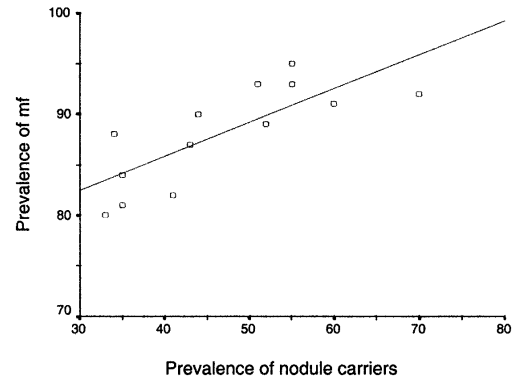


FIGURE 1. Association between prevalence of male nodule carriers and prevalence of infection ( $R^2 = 0.603$ ,  $P = 0.002$ ). mf = microfilaria.

with ivermectin (a nodule prevalence in males  $\geq$  40%, a CMFL  $\geq$  20 mf/mg skin, and an mf prevalence  $\geq$  60%).<sup>2</sup>

The study was approved and ethically cleared by the Ugandan Ministry of Health and the District Medical Director of Kabarole district. All study participants received an explanation of the study in the Rutooro language. The informed consent was read in the local language and the persons who participated in the study signed the consent form. Parents signed on behalf of adolescents under the age of 18 years. Participants unable to sign for themselves were assisted by a witness, who verified the subject's agreement and noted it in writing on the consent form. In addition to the individual consent, the village chiefs of the thirteen villages in Kigoyera Parish gave their consent on behalf of their communities.

RESULTS

We found a strong positive association in the 13 villages between the nodule prevalence in males more than 20 years old and the prevalence of mf carriers in the population. Similarly, the nodule prevalence in young males was also associated with the CMFL in the 13 communities. There was no association between the nodule prevalence and leopard skin and between the nodule prevalence and hanging groins. The regression lines are shown in Figures 1 and 2.

We also tested the association between the nodule prevalence in males and females as the dependent variable and the above noted parameters as the covariates. The association between nodule prevalence in males and females and prevalence of mf and CMFL was also significant, but had lower  $R^2$  values compared with the relationship with the nodule prevalence of only males as the dependent variable (Figures 3 and 4).

We also examined the relationship between prevalence of nodules in males and the prevalence of onchodermatitis in the 13 villages. We found a significant positive association between the nodule prevalence and the prevalence of dermatitis when data were aggregated according to the 13 villages of the Parish ( $R^2 = 0.540$ ,  $P = 0.004$ ). In contrast to the findings from West Africa, the nodule prevalence in males was not associated with any of the ophthalmologic parameters. In addition, there was no relationship between nodule prevalence and prevalence of leopard skin, and no relationship between the prevalence of nodules and the prevalence of hanging groins.

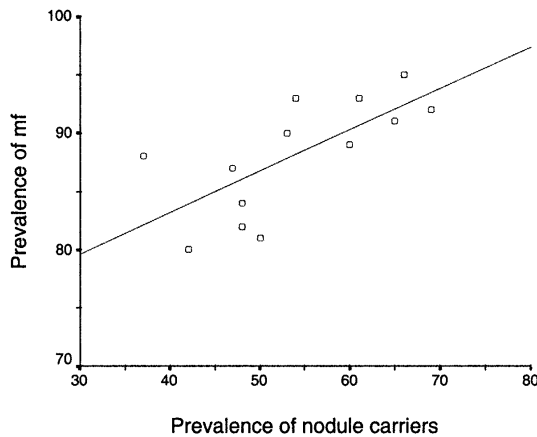


FIGURE 2. Association between prevalence of male and female nodule carriers and prevalence of infection ( $R^2 = 0.491$ ,  $P = 0.008$ ). mf = microfilaria.

Using WHO criteria and cut-off points for urgent and immediate intervention with ivermectin from savanna villages,<sup>2</sup> we found the following values for sensitivity and specificity for the nodule palpation test: for a cut-off point  $\geq 60\%$  microfilarial prevalence, the sensitivity for nodule palpation was 92.3% and the specificity was 100% in correctly classifying those villages that were eligible for urgent ivermectin treatment. Using the CMFL with a cut-off point of 20 mf/snip skin and the same threshold level of nodule prevalence, the same values for sensitivity and specificity were obtained. In both cases, 12 of the 13 villages would have been correctly identified as needing to receive urgent ivermectin mass treatment, using only nodule palpation and no invasive diagnostic procedures such as skin snipping.

#### DISCUSSION

Based on the data from the 13 villages in Kigoyera Parish, we found a strong association between the prevalence of nodules and the prevalence of infection with *O. volvulus* (Figures 1 and 2). Similarly, we found an association between the nodule prevalence and the intensity of infection (CMFL). The association between the nodule prevalence and other onchocerciasis parameters (nodule prevalence, CMFL) has been shown in many studies from West Africa, where *S. damnosum* s.l. is the transmitting vector. Kollo and others found in southern Cameroon a significant correlation between the nodule prevalence and the prevalence of infection and between the nodule prevalence and the CMFL with  $R^2$  values of 0.41 and 0.38, respectively.<sup>8</sup> Whitworth and Gemade observed in Benue State, Nigeria that nodule prevalence correlated more closely with microfilarial prevalence than with CMFL, which is similar to our findings.<sup>9</sup>

Our coefficient of variation ( $R^2$ ) values were higher when compared with those in the studies of Kollo and others and Whitworth and Gemade, indicating overall a stronger correlation between the prevalence of nodules and the mf prevalence and the CMFL. The suitability of nodule palpation for the identification of villages eligible for urgent ivermectin intervention is further confirmed by our data, which showed a high sensitivity of 92.3% and a high specificity of 100% of nodule palpation in determining a microfilarial prevalence of 60% or higher. Sensitivity and specificity in our study were

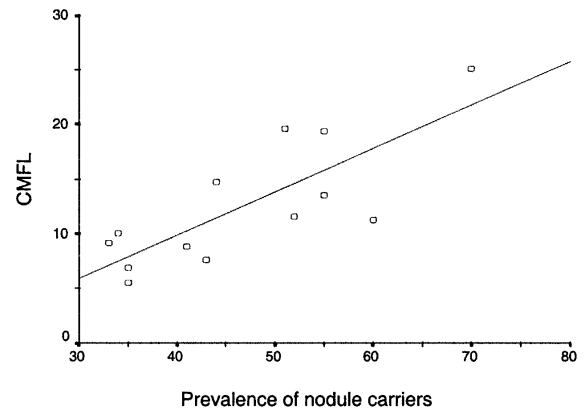


FIGURE 3. Association between prevalence of male nodule carriers and community microfilarial load (CMFL) ( $R^2 = 0.620$ ,  $P = 0.001$ ).

higher than those in the studies of Kollo and others Whitworth and Gemade from West Africa noted earlier. Our data further showed that nodule palpation in males yields a nodule prevalence that is more strongly associated with the other onchocerciasis parameters noted earlier. We conclude that nodule palpation in males is a suitable examination method in correctly identifying communities in *S. neavei* s.s.-transmitted, endemic onchocerciasis areas for urgent intervention with ivermectin treatment. Our data did not allow us to determine the positive and negative predictive values of nodule palpation.

We also found a significant positive association between nodule prevalence and prevalence of onchocercal skin disease. The coefficient of variation for this association in our study (0.54) was higher than those in the studies of Kollo and others in Cameroon (0.42) and of Whitworth and Gemade in Nigeria (0.15). Our finding may indicate that the prevalence of nodules is also a valid predictor of the burden of onchocercal skin disease in areas where *S. neavei* s.s. is the transmitting vector.

Our study had three limitations. First, since the sample size of the villages is rather small, there may be problems in generalizing the study results to other areas in Uganda or elsewhere. Second, the validity of our findings is limited to villages with areas of high transmission of onchocerciasis.

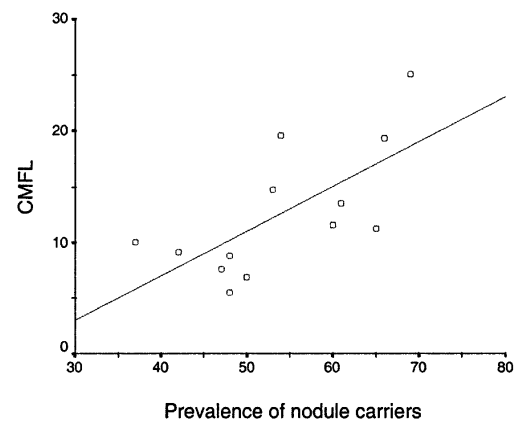


FIGURE 4. Association between prevalence of male and female nodule carriers and community microfilarial load (CMFL) ( $R^2 = 0.460$ ,  $P = 0.011$ ).

Therefore, the validity of nodule palpation cannot be related to mesoendemic or hypoendemic areas of onchocerciasis, where the microfilarial prevalence is lower than in our sample. The reason we did address this limitation in our study was that in the original study data from hypoendemic and mesoendemic onchocerciasis areas were not collected. (The main objective of the original study was to determine the clinical and parasitologic features of *S. neavei*-transmitted onchocerciasis, not to prove that nodule palpation is a valid tool for the assessment of the endemicity in this focus.) Third, in the original data, some cases of nonspecific dermatitis may have been misclassified as onchodermatitis, which could have biased some of the study results, influenced the correlation between nodule palpation and onchodermatitis, and overestimated the prevalence of onchodermatitis. However, since all investigators in the original study had extensive experience in the diagnosis of onchocercal skin disease, we do not believe that those misclassifications occurred frequently.

In conclusion, we conclude that to the best of our knowledge we have reported for the first time that nodule palpation is a useful tool in identifying communities eligible for urgent ivermectin mass treatment in areas where *S. neavei* s.s. is the transmitting vector of *O. volvulus*. We also suggest that nodule palpation may be used to rapidly assess/identify communities with a high burden of onchocercal skin disease for appropriate intervention measures. These are important findings for the control of onchocerciasis in areas of central and eastern Africa, where the forest form of onchocerciasis prevails, where *S. neavei* s.l. is the main transmitting vector, and where general health workers rather than specialists are the backbone of onchocerciasis control. As the large-scale African Program for Onchocerciasis Control is set up to deliver ivermectin mass treatment intervention strategies in many areas of Africa outside of the OCP area in West Africa,<sup>10</sup> the need to identify high risk communities with simple and inexpensive diagnostic measures becomes imperative. Simple nodule palpation enables control teams to ensure that communities in urgent need of treatment with ivermectin are identified without delay and are treated.

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