HUMAN ONCHOCERCIASIS IN SIX VILLAGES IN WESTERN BAHR EL GHAZAL STATE, SOUTH WEST SUDAN: THE RELASHIONSHIP BETWEEN PALPABLE NODULES, SKIN AND OCULAR LESIONS PREVALENCE.

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ABSTRACT:

This study analyses data from Rapid Epidemiological Mapping/Rapid Assessment (REMO/REA) studies done in Western Bahr El Ghazal State, south west of Sudan, in November 1997. Our aim was to give a detailed picture of Onchocerciasis in that state, investigate the relation between the prevalence of three onchocerciasis manifestations, namely palpable nodules, skin and ocular lesions, analyze the same three prevalences with respect to age and determine whether the nodule status of an individual patient and the nodule prevalence in his village have any predictive value for his risk to develop an ocular and/or a skin lesion. All the six villages were hyperendemic for onchocerciasis with considerable variation between the villages with regards to the three onchocerciasis manifestations. Skin and ocular lesions prevalence were found to correlate roughly with nodule prevalence, although the latter seemed to underestimate the skin lesions prevalence. Ocular lesions prevalence increased considerably with age while skin lesions and nodule prevalence were high (>45%) in all age- groups. Logistic regression analysis showed that the probability of developing a skin lesion correlated negatively with the patient's nodule status but positively with his village nodule prevalence and the interaction between his age and his nodule status. Logistic regression also showed that the probability of developing an ocular lesion correlated with the patient's age, village nodule prevalence and the interaction between the two. This study confirms the fact that onchocerciasis prevalence obtained by nodule palpation can be used for rapid assessment purposes, bearing in mind that nodule prevalence may underestimate that of skin lesions. The study also points out that selective treatment based on nodule diagnosis can be problematic specially that the relationship between the nodule, skin and ocular lesions prevalence is not a straight forward one.

INTRODUCTION

Palpable subcutaneous nodules, severe itching, disfiguring skin lesions, blindness, abandonment of fertile river valleys and social ostracism are some of the consequences of infection with *Onchocerca volvulus,* the worm which causes onchocerciasis or "river blindness". The disease is transmitted by the bite of a female black fly family *Simuliidae* which breeds in fast flowing rivers. Onchocerciasis is a serious public health problem and an obstacle to socio-economic development in areas where it is endemic.

Eighteen million people are infected with onchocerciasis, 99% of whom live in Africa (1). One of the affected African countries is Sudan where it is estimated that more than 2 million people are infected with the disease in addition to another one million who are potentially exposed to infection (2).

The public health importance of onchocerciasis, both in terms of skin and ocular lesions, is directly related to the degree of endemicity of infection in the community (3). Studies aiming at identifying and mapping-out endemic areas described as high risk, and thus in great need for disease control measures, and having hyper- (nodule prevalence >40%) or meso-endemic (nodule prevalence>20%) levels of the disease (3) were carried out in many areas of Sudan. These studies are called *Rapid Epidemiological Mapping of Onchocerciasis* (REMO) and *Rapid Epidemiological Assessment* (REA) studies. The results showed that one of the most important regions in Sudan, in terms of disease severity and high prevalence, is in Western Bahr El Ghazal State (WBGS), in the south-western region of Sudan (2).

The present study aims at giving a detailed description of the disease picture in WBGS using REMO/REA data. It investigates the relation between palpable nodules prevalence and skin and ocular lesions prevalence. Nodules, skin and ocular lesions prevalence are also analyzed with respect to age. Another

objective of the present paper is to find out whether the nodule status of a patient is of any predictive value for the presence of an ocular and/or a skin lesion.

MATERIALS AND METHODS:

We analyzed data from REMO/REA activities carried out in six villages in Western Bahr El Ghazal State, south west Sudan, in November 1997 (see map, to be included later). Details of the actual procedures involved in REMO/REA studies are provided elsewhere (3).

The REMO/REA activities were done by trained Medical Assistants with special training in onchocerciasis, for not less than 10 years, and who had attended quality assurance courses the most recent of which was held in Sudan in September 1997. They were supervised by trained medical doctors from the *National Onchocerciasis Task Force* (NOTF)-Sudan. The search for nodules was done in a systematic order and depending on a body map. All examiners were trained in identification of the texture of onchocerciasis nodules, in addition all questionable nodules were checked by the supervising doctors who determined whether or not they were to be included.

Age of the examined participants was determined by asking the individuals themselves, but since it is known from past experience that in those rural areas self-reported age is not accurate, especially in the age-group between 25-70 years, age was in many instances estimated.

In total 300 individuals were examined, 50 individuals in each of the six villages. The age range of the participants was between 10- 70 years. For each individual examined the following data were recorded: name, age, sex, onchocerciasis nodules: present/absent (sometimes the number of nodules a patient had were also recorded), onchocerciasis eye lesions: present/absent, and onchocerciasis skin lesions: present/absent. There were only very few missing observations.

Data were analyzed both on a village level and on an aggregated level. Logistic regression analysis was applied to the aggregated data to relate the presence of skin and/or ocular lesions to the nodule status of the patient and the prevalence of

nodules in his village. Age was used as a covariable and interaction terms were also included in the analysis. Inclusion or exclusion of variables was based on a likelihood ratio test, using a 5% significance level and starting with the full model. SPSS (version 7.5 for Windows) was used to estimate coefficients and standard errors.

RESULTS:

In each of the six study villages, 50 individuals were examined resulting in a total study sample of 300 individuals. Age of the participants ranged between 10- 70 years (note: in a typical REMO/REA study, only individuals 20 years of age or older are examined); 94% were males and only 6% were females. Recording of observations was efficient with very few missing data.

As an overview of the Sudanese REMO/REA data, *fig 1* describes the onchocerciasis picture in the six study villages. According to the REMO/REA definitions of hyper- and meso- endemic areas of onchocerciasis, the figure shows that there are five hyper-endemic villages and only one meso-endemic village, considering only the prevalence of palpable onchocerciasis nodules (range from 30-80 %). Ocular lesions prevalence had a range of 10-80 % and that of skin lesions was 50-95 %.

In *fig. 2* the prevalence of skin and ocular lesions is plotted against the nodule prevalence. The skin lesions prevalence correlates much better with that of the nodules than does the ocular lesions prevalence. A further observation is that the prevalence of skin lesions is higher than that of nodules in all the six villages.

We also studied the relationship of the three onchocerciasis manifestations with age. *Fig 3* shows the combined results of the six villages. Skin lesions and nodule prevalence were high (>45%) in all age-groups including the youngest age-group. A clear relationship with age was found only for ocular lesions, the prevalence of which increased considerably with age. As a first step to investigate if correlation on a village level also imply correlation on an individual level, *figs 4* shows the age-specific skin and ocular lesions prevalence among those with (*4A*) and those without (*4B*) nodules. The figures showed the following results: the first being that skin lesions prevalence was *higher* among patients with *no* nodules (especially in the age-group 10-29 years) than among those with nodules; the

second was that for patients with no nodules skin lesions prevalence tended to *decrease* with age.

Figs 4 A and B demonstrated that the relationship between the three onchocerciasis manifestations was not straightforward, therefore we employed a logistic regression analysis to identify which factors determined an individual's risk/ probability to develop an ocular and /or a skin lesion, *fig 5 and table 1.* *Fig 5* shows estimated age-specific ocular and skin lesions prevalence on the basis of the logistic regression results. *Table 1* shows the odds ratios (and 95% CI) resulting from the logistic regression models relating the presence of skin-lesions or eye-lesions in a person to his age, his nodule-status: without nodule (nod=0) and with nodule (nod=1), and the prevalence (fraction) of nodules in the village (vnod). Also the interaction between these variables is considered. Results are shown for the full models (i.e., including all variables) and for the minimal models obtained after backward elimination using a likelihood-ratio test (5% significance level as exclusion criterion). The resulting minimal models were as follows:
For the probability/risk of developing a skin lesion:

P(skin) = F(Nodule + Nodule*Age + Vnod + Constant);

For the probability/risk of developing an ocular lesion:

P(Eye) = F(Age + Vnod + Vnod*Age + Constant).

These minimal models can be explained as follows:

- Skin: the probability to have a skin lesion is strongly positively associated with the village nodule prevalence, i.e. Vnod, (which is employed in REMO/REA studies as a measure of endemicity). There is a positive association with age only for those with one or more nodules. In addition, there is a negative association with the presence of nodules particularly for young ages (odds ratio for the variable Nodule <1).
- Eye: the probability to have an ocular lesion is also strongly associated with the village nodule prevalence (Vnod). An association with age is also observed

here. The positive correlation with Vnod and age tend to decrease when both Vnod and age increase (odds ratio of the interaction term Vnod*Age <1).

DISCUSSION:

This study shows that five of the six Sudanese villages studied are hyperendemic for onchocerciasis and one is meso-endemic. In addition considerable variation between the villages with regards to the different onchocerciasis manifestations was found. Both of the above findings are in agreement with the literature (2).

Regarding the relationship between nodule prevalence, skin and ocular lesions prevalence, both skin and ocular lesions prevalence correlate roughly with nodule prevalence. This confirms that nodule palpation can be used for rapid assessment purposes, as has been recommended by the Pan-African study group on onchocercal skin disease report on their multi-country study on the importance of onchocerciasis skin disease (11). However, nodule prevalence could underestimate skin lesions prevalence. This has also been shown by the results of several other studies (2,4,5,6,7) where nodule prevalence was consistently lower than that of skin lesions. On the other hand, two other studies (8,9) reported prevalence values which were higher for nodules than for skin lesions, while a third study (11) reported a good correlation between the prevalence of the two manifestations. The fact that nodule prevalence could underestimate skin lesions prevalence might become problematic in situations of meso- or hypo-endemic onchocerciasis, and where skin disease is the main presentation of onchocerciasis. The reason behind this is that some programmes such as the African Programme for Onchocerciasis Control (APOC), which uses the new drug Ivermectin (Mectizan) for control of onchocerciasis in many African countries, consider a site as in need of control only if that site is meso- or hyper- endemic for onchocerciasis. Also, the drug dose and/or regimen might differ according to the level of endemicity. Thus, in the case of underestimating the endemicity of onchocerciasis in a site, that site might become excluded from a control

programme although it is in fact meso- endemic, or it might be treated as a meso-endemic site although it is actually hyper- endemic for onchocerciasis.

An age-specific trend was most apparent with ocular lesions. This observation has been reported before in other studies (5, 6, 10). For the other two onchocerciasis manifestations studied, i.e. skin lesions and palpable nodules no clear cut age-specific trend could be observed. These findings reflect what is known about the natural history of onchocerciasis, namely that ocular lesions need some time to develop and become manifest, thus they are more prevalent in older age-groups (12). On the other hand, skin lesions can present as acute as well as chronic lesions, which may explain the approximately equal distribution across all age-groups. Hence, the division of skin lesions into types and grades of severity could result in a more clear and precise description of its age-specific trend.

Moving on to the examination of variables which could be used to define an individual patient's risk/probability to develop an ocular and/or a skin lesion, our logistic regression analysis of the data indicated that:

a) Logistic regression showed a positive correlation between the probability of developing a skin lesion and the interaction between the age and the nodule status of the patient. This implies that for young children the risk of developing a skin lesion is higher for those *without* a nodule than for those *with* a nodule, while for older people this may reverse, *fig5*. In addition, the probability/risk of developing a skin lesion correlates with the village nodule prevalence (the latter is used in REMO/REA studies as a measure of endemicity). This is not surprising given the good correlation between skin lesions and nodule prevalence. However, the same probability correlates *negatively* with the nodule status of the patients, in particular young ones. An explanation to this might be that young and/or recently infected patients whose immune system is more active, or less tolerant to the infection, react more vigorously to onchocerciasis filariae and, thus, have more reactive skin lesions with less

nodules (12,13). The reverse occurs in patients who are older, with a longer duration of infection and/or less reactive immune systems (12).

b) The probability of having an ocular lesion does not correlate with the nodule status of the person. There is only a positive relation with the person's age, as explained above, and his village nodule prevalence. The relationship between ocular lesions and the presence of *onchocerca volvulus* microfilariae in the eye (which can be viewed as a reflection of the patient's nodule status) in sot a straightforward one. Thus it does not immediately follow that the mere presence of microfilariae in the eye leads to the development of ocular lesions. A lot of mechanisms, which are not yet fully understood, come into play. One known fact is that, just as is the case for skin disease, developing ocular lesions seems to depend primarily on the degree of response of the patient's immune system to the presence of microfilariae in the eye (12). Many factors influence this immune system reaction to infection, e.g.: the village nodule prevalence which is used as a measure of disease endemicity which, in turn, reflects the status of the "Herd" immunity to onchocerciasis.

The attempt to relate on an individual level the disease outcome (skin and/or ocular lesions) to a simple diagnosis like the presence of nodules has, to our knowledge, not been done before. It could provide an important tool for clinicians and other health personnel who are dealing with onchocerciasis patients in general and specifically in endemic areas. It translates, and explains, the general endemicity levels of the patient's locality into specific, individually meaningful probabilities and/or risk values. Furthermore, it confirms that for community treatment REMO/REA is fine (bearing in mind that nodule prevalence may underestimate skin lesions prevalence), while pointing out that selective treatment based on nodule diagnosis is indeed problematic. In addition it might prove useful if used to describe and assess the burden of disease and/or the impact of control strategies on the individual patient's level. This can be done by applying the same, or similar, analytical procedures as utilized in this paper to analyze data collected

from the same or similar villages after a suitable period of disease control (N.B. recently it has started to become a trend to perform "impact assessment studies" to evaluate the magnitude of effect of many control programs implemented by organizations such as the World Health Organization).

A limitation to the immediate generalization of our results is that we analyzed REMO/REA data which are, by design, not very detailed. For example, it does not distinguish between the different types and severity grades of skin and ocular lesions. There is a need to address and verify the results of this study in future research work perhaps applying the same methods to REMO/REA data of other countries, including areas with low endemic levels of onchocerciasis. Also, similar analytic methods could be applied to data sets that differentiate skin and ocular lesions into types and grades of severity.

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Fig. 1: Prevalence of Onchocerciasis by Diagnosis

Remo Data, Sudan 1997

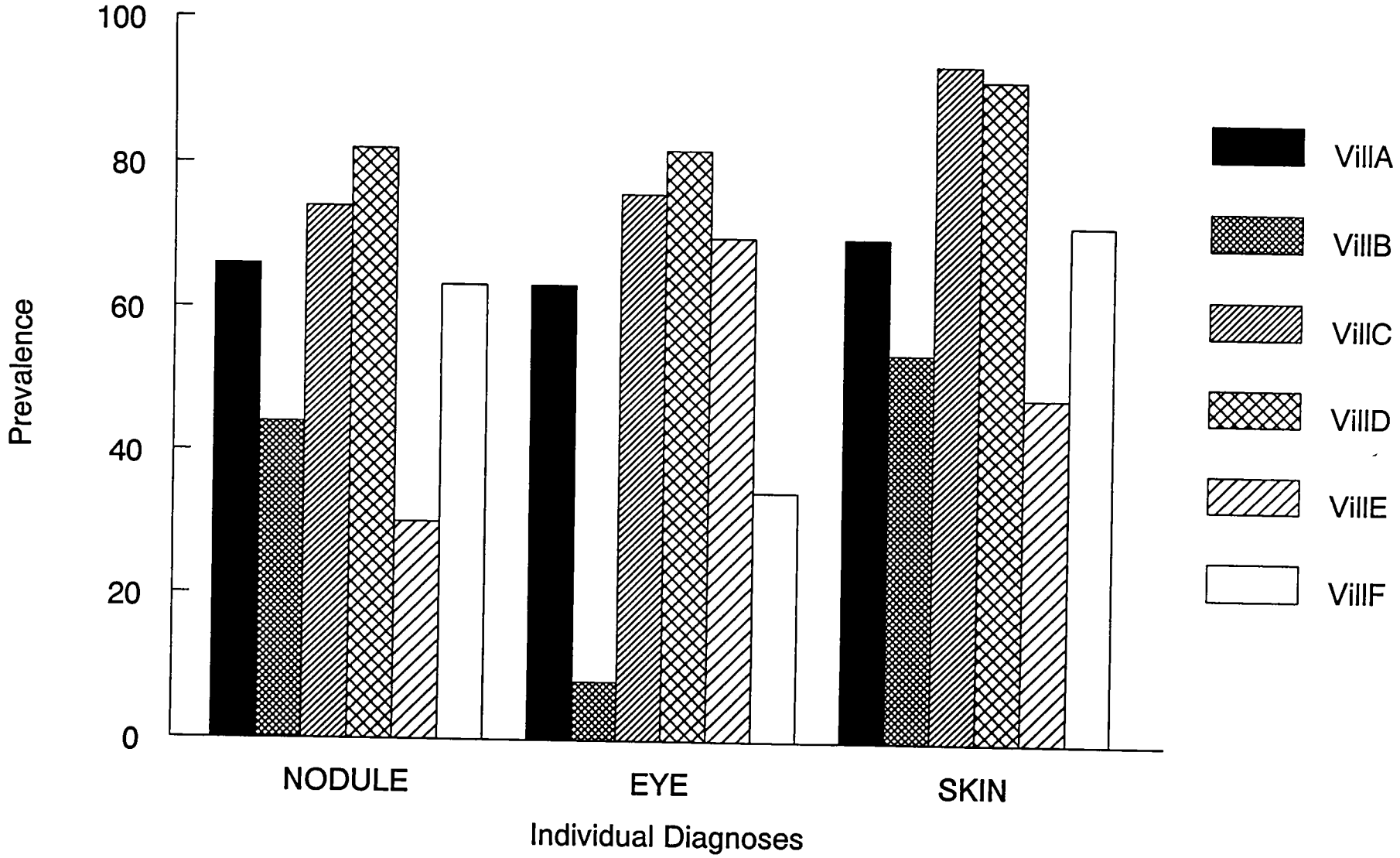

Fig 2: Relationship Between Nodule Prevalence and Skin & Eye Prevalences

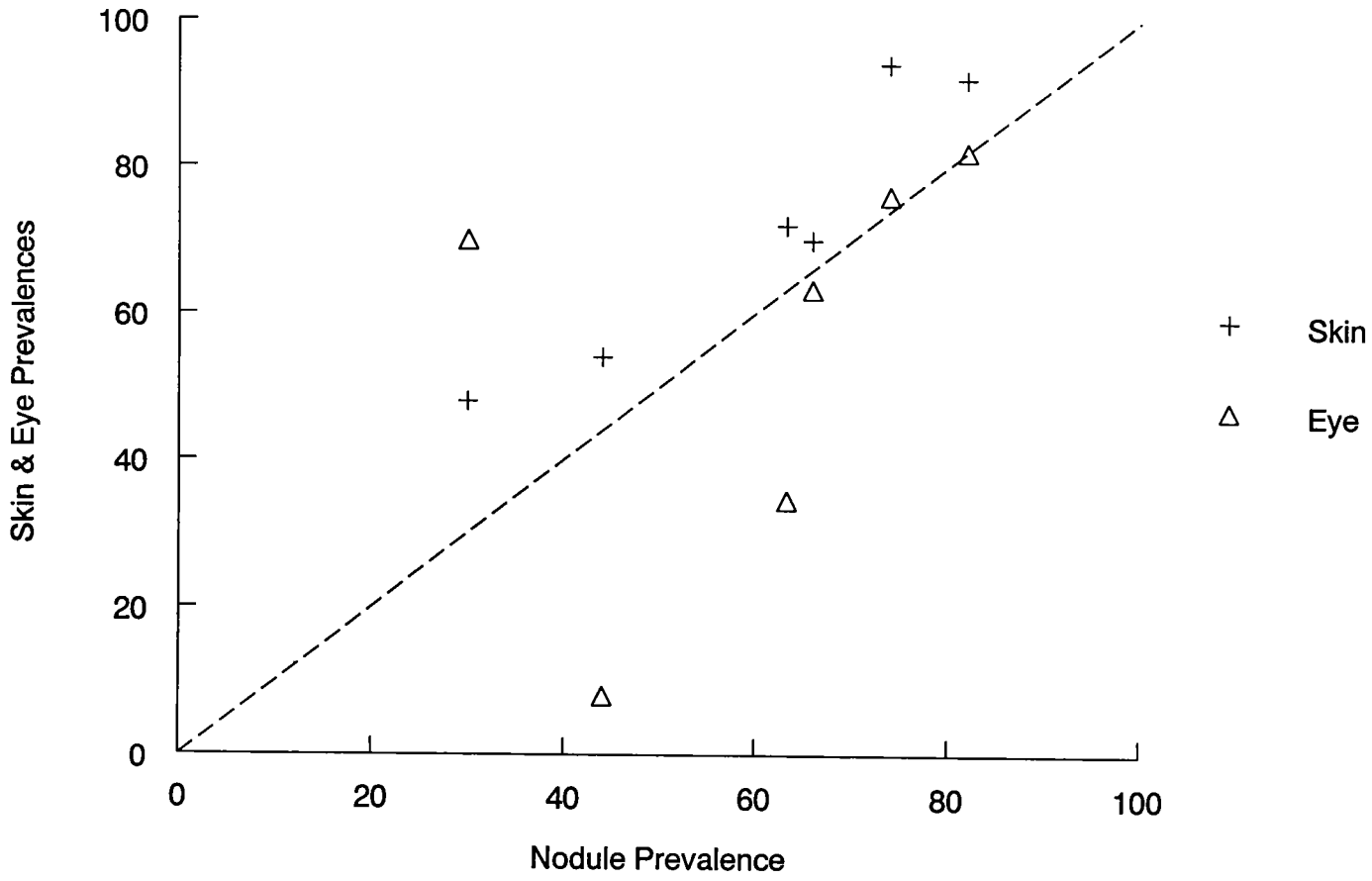

Fig. 3: Diagnoses' Prevalences by Age Groups
(Aggregated Data)

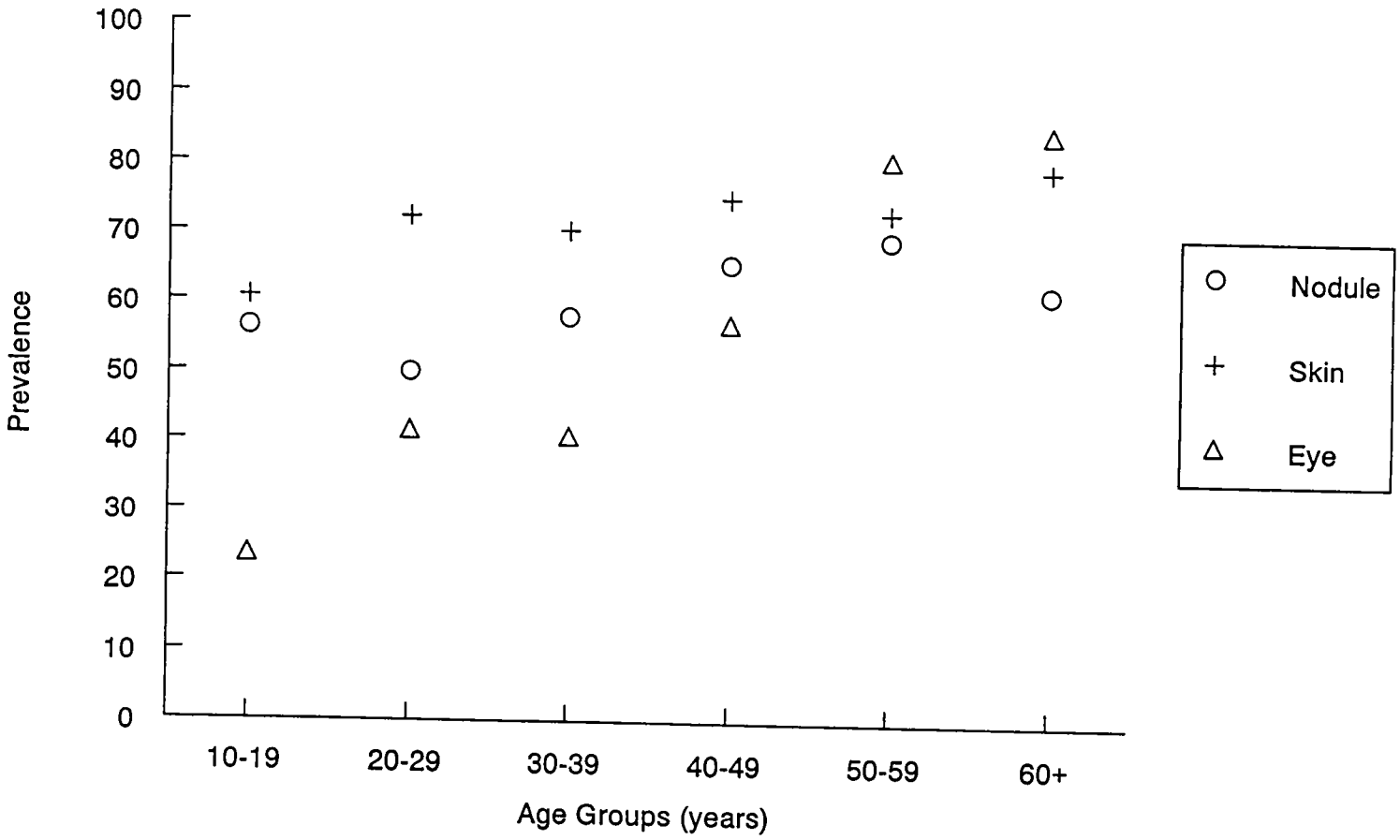

Fig. 4A: Skin & Oc ular Lesions Prevalences By Age Group

Among Patients With Nodules

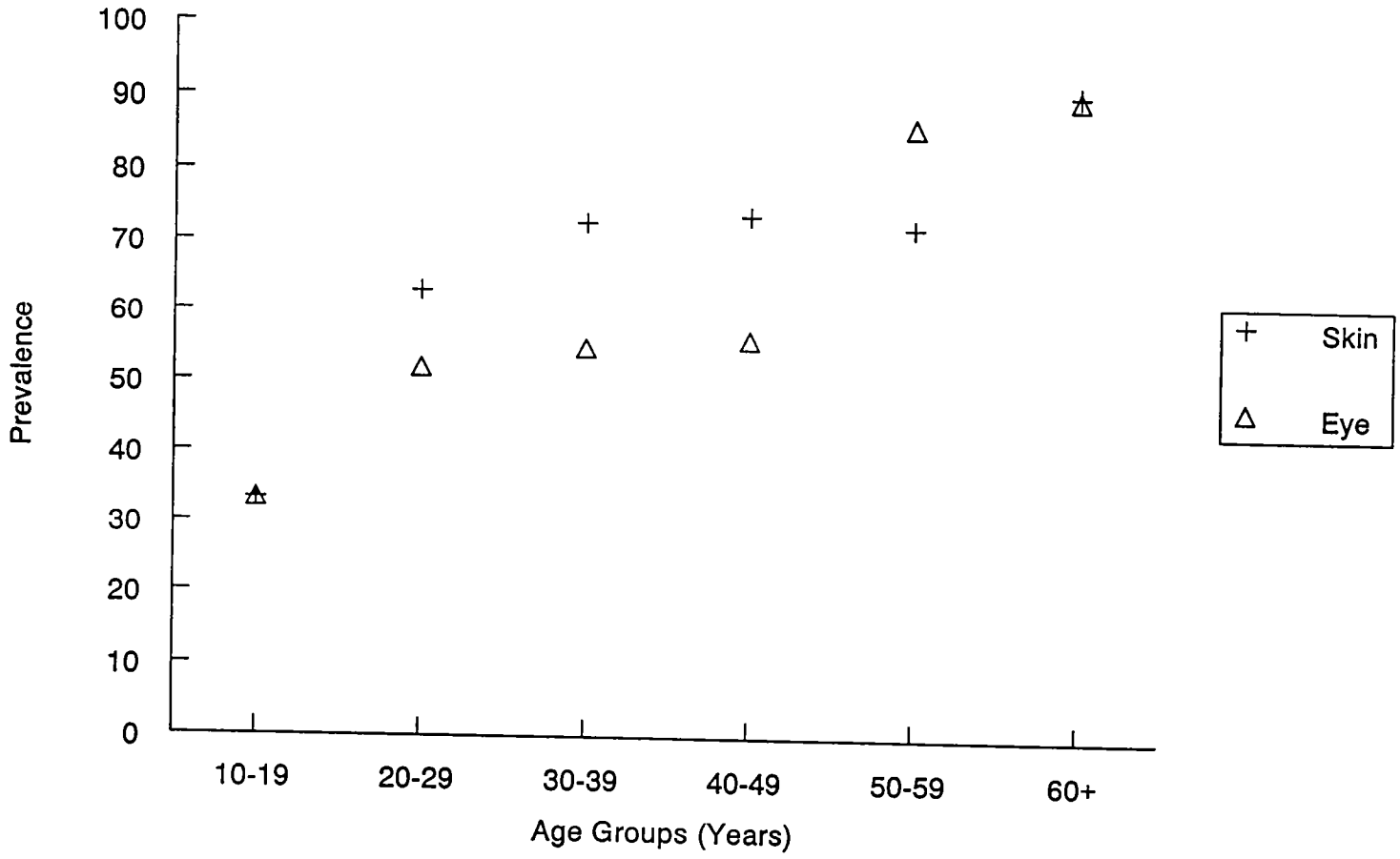

Fig. 4B: Skin & Ocular Lesions Prevalence by Age Group

Among Patients With No Nodules

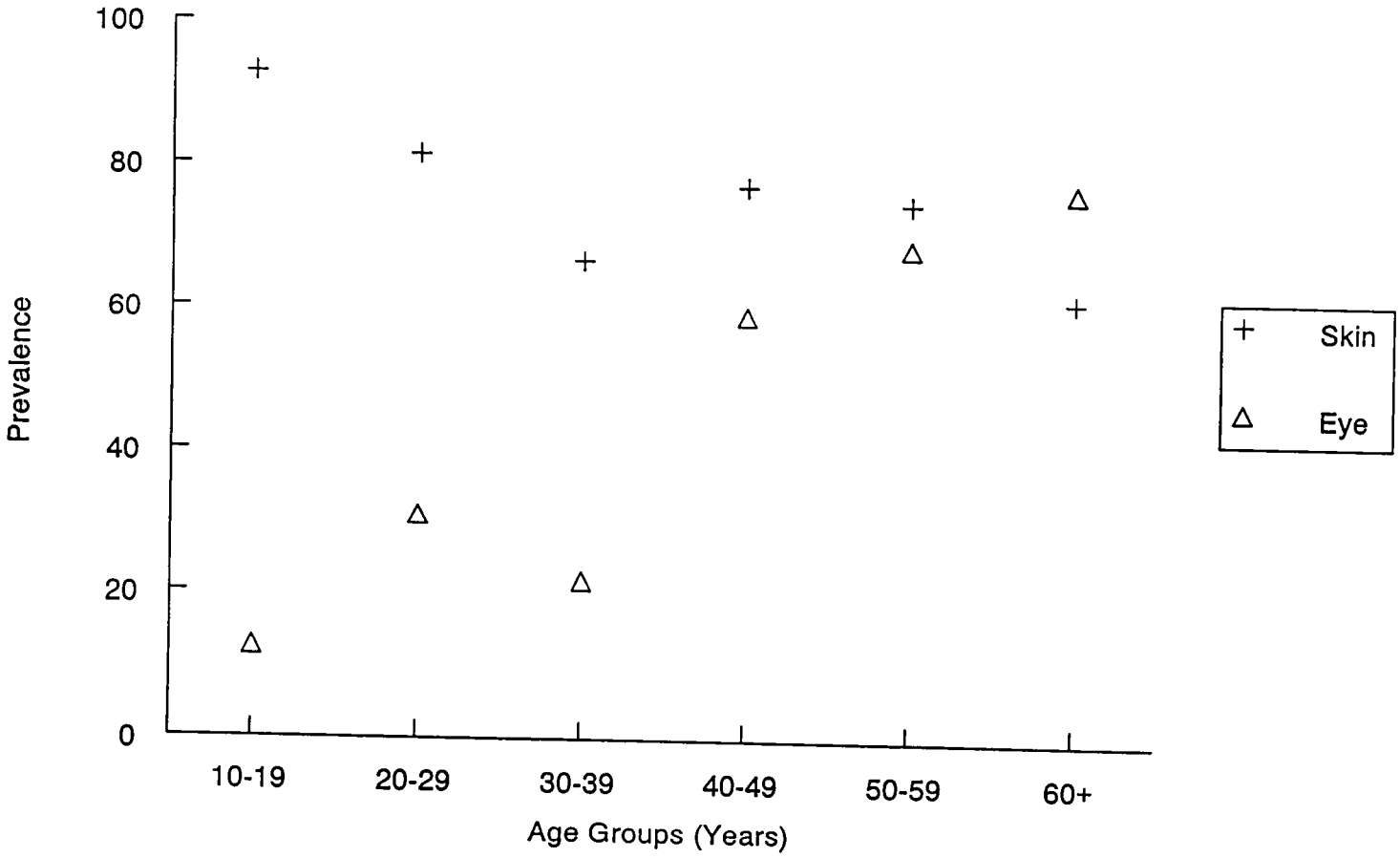

Fig. 5: Schematic presentation of Logistic Regression results

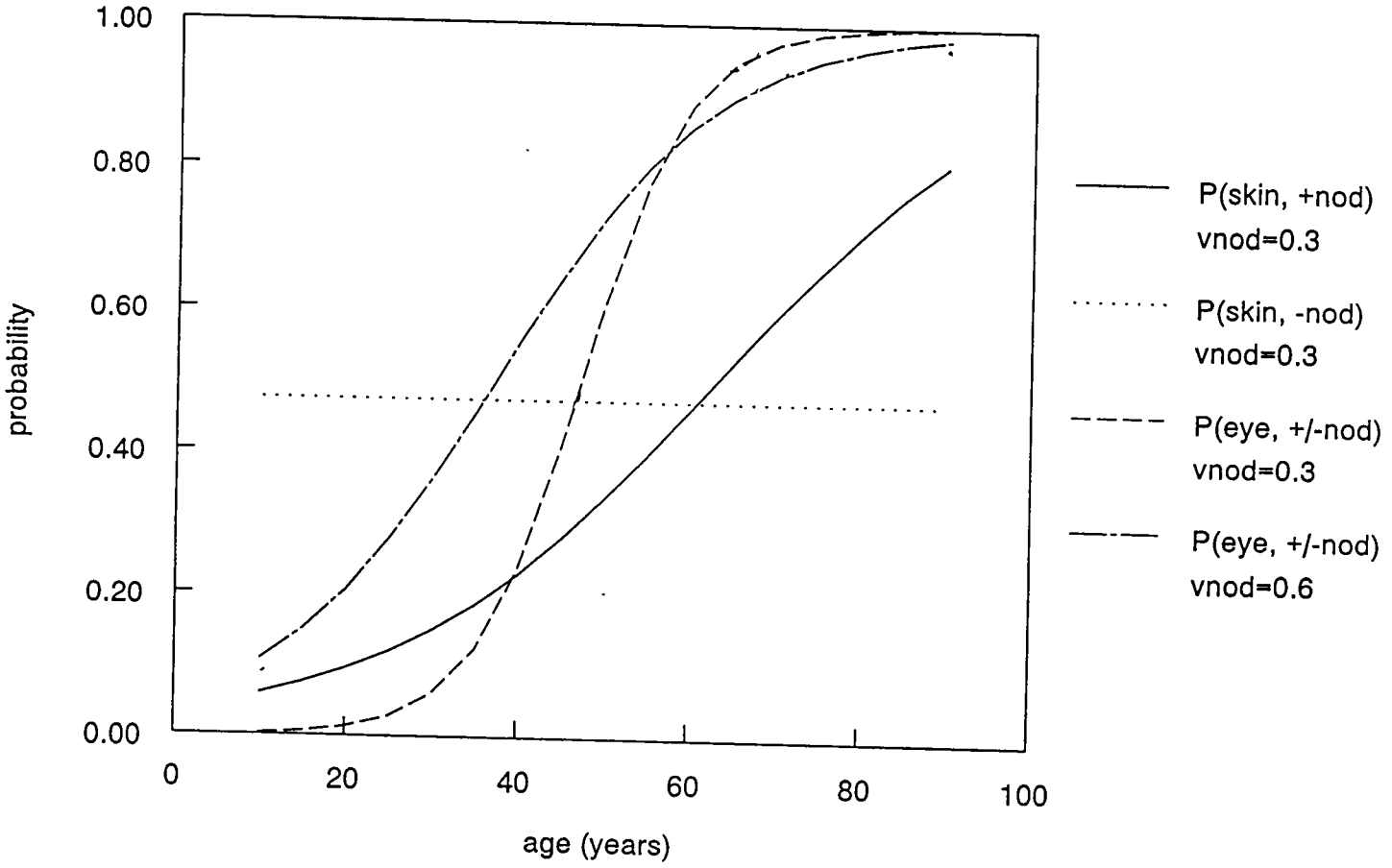

Table 1 Odds ratio's (and 95% CI) resulting from the logistic regression models relating the presence of skin-lesions or eye-lesions in a person to his age, his nodule-status: without nodule(nod=0) and with nodule (nod=1), and the prevalence (fraction) of nodules in the village (vnod). Also the interaction between these variables is considered. Results are shown for the full models (i.e., including all variables) and for the minimal models obtained after backward elimination using a likelihood-ratio test (5% significance level as exclusion criterion).

Variable	Skin lesion		Ocular lesion	
	Full model	Minimal model	Full model	Minimal model
age	0.95 (.88 - 1.03)		1.3 (1.2 – 1.4)	1.3 (1.2 – 1.4)
nod	0.019 ($<10^{-3}$ - .48)	.038 (.011 - .13)	1.9 (.090 – 42)	-
vnod	8.7 (.01 - $>10^3$)	750 (107 - $>10^3$)	$>10^3$ ($>10^3$ - $>10^3$)	$>10^3$ ($>10^3$ - $>10^3$)
age x nod	1.1 (1.0 – 1.1)	1.1 (1.0 – 1.1)	1.0 (.95 – 1.0)	-
age x vnod	1.1 (.94 - 1.3)	-	.76 (.65 - .88)	.76 (.65 - .88)
nod x vnod	4.5 (.072 - 282)	-	.61 (.019 – 20)	-

- means not included

Figure legends:

1. Prevalence of each of the three onchocerciasis manifestations (nodules, ocular lesions and skin lesions) by village.

2. Relation between the nodule prevalence and the prevalence of skin-lesions (+) and the prevalence of eye-lesions (triangle). The dotted line represents a 1:1 relation.

3. Relation of the three onchocerciasis manifestations with age. Data of all 6 villages have been taken together.

4A. Relationship of skin and ocular prevalence with age for patients with a nodule (all villages together)

4B. Relationship of skin and ocular prevalence with age for patients without a nodule (all villages together)

5. Estimated age-specific prevalence of skin-lesions (solid line for those with a nodule; dotted line for those without a nodule) and ocular lesions (dashed line for a village with a nodule-prevalence of 30%; dot-dashed line for a nodule prevalence of 60%).