Evidence for Suppression of Transmission in the Oaxaca Focus in Mexico

prevalence in skin biopsy specimens > 60%) were found in the Oaxaca focus.

The present entomologic study was conducted during the 2004 transmission season, and the serologic study was carried out on samples collected in both 2001 and 2004. The four

directed to the MBP might have confounded the assay. To control for this, anti-MBP assays were carried out in parallel and subtracted from the recombinant antigen values. The mean of eight optical density values of positive control sera from a pool of high-responding Mexican onchocerciasis sera was used to correct all ELISA values for each plate. We previously described the utility of this ELISA for detecting exposure to infection in a sentinel cohort from Las Golondrinas of the Southern Chiapas focus under treatment with ivermectin.[15] The ELISA is a sensitive tool for detection of children pre-patently infected or who have been exposed to infective larvae because the Ov7 and Ov11 antigens are present in third-stage larvae.[16,17]

Antibody prevalence was defined as the proportion of antibody-positive results among persons who had optical values equal to or greater than the cut off value. The cut-off for classifying a sample as positive was set at the mean of the 30 negative controls plus 7 standard deviations.[18] Test specificity at this cut-off value was 100% and sensitivity was 96% when compared with the skin snip test,[19] and 97% when compared with a seropositive reference collection.[20]

Data analysis. Because . , s.l. females were not collected throughout the year, it was not possible to precisely calculate the ATP. However, in Mexico, the level of transmission during the peak of transmission season was very low (because of the effect of 11 years [22 rounds] of treatment with ivermectin). The value of transmission potential outside of the peak transmission period (when the fly population is low) is therefore probably zero or near zero. Therefore, the

negative for . , which suggested a low or nonexistent rate of parasite-vector contact, and a corresponding lack of transmission. For this reason, most of the head pools from these communities were not examined further. However, a randomly selected sample of 28 head pools of La Chichina was screened to confirm this supposition. As expected, all of these pools were also negative in the PCR assay.

In Santiago Lalopa, one pool of bodies (of the first 152 pools or 7,600 flies tested) was PCR positive, which indicated parasite-vector contact in this community. However, no positive head pools were found (165 pools screened or 8,250 flies), which resulted in a prevalence of infective flies of 0 (95% upper limit [UL] = 0.46/2,000 flies).

In La Esperanza, as in Santiago Lalopa, a body pool was positive in the initial screening, which suggested parasite-vector contact. Subsequent screening of 169 head pools (8,450 flies) resulted in a single confirmed positive pool, which resulted in a calculated prevalence of infective flies of 0.35/2,000 flies (95% UL = 0.92/2,000 flies), and a calculated transmission potential of 6.7 third-stage larvae per person per year.

The number of flies collected in each community ranged from 2,450 to 8,500, which was less than 10,000. Thus, when separated by community, the number of vectors collected was not sufficient to comply with the WHO guideline of having at least 10,000 flies tested from each community. However, in all cases, the sample was sufficient to exclude 1/2000 in the UL of the 95% CI. Taken together, the 367 head pools (18,350 flies) were screened from the four sentinel communities of the Oaxaca focus, which resulted in an overall prevalence of infective flies of 0.27/2,000 (95% CI = 0.01–0.6/2,000) flies, which met the OEPA current criterion for "absence or near absence" of transmission. None of the 117 children < 10 years of age seroconverted in the four sentinel communities of the Oaxaca focus (Table 2), which resulted in an estimated exposure incidence of 0%.

DISCUSSION

The data in our study suggest that transmission of . - has been suppressed in the Oaxaca focus of Mexico. During the four-year period encompassed by this study (2001–2004), none of the initially seronegative children seroconverted as assayed by ELISA had seroconverted. The absence of contact with the parasite in this cohort of children ≤10 years of age (i.e., subjects born after the implementation of the ivermectin distribution program) indicates that none had been exposed to . , which suggested that the level of exposure to the parasite is now quite low in this area. This finding is consistent with those of a previous parasitologic study, which demonstrated that consecutive treatment with ivermectin has resulted in a dramatic decrease of the prevalence of skin microfilariae and nodules in Oaxaca, beginning as early as 1998.[21] Despite these promising findings in the human population in 1998, the first large-scale entomologic study of transmission in this area, which was conducted in 2001 after six years of mass administration of ivermectin, demonstrated that three of four sentinel communities still had evidence for ongoing transmission.[4] In 2001, the prevalence of infective flies was 1.6/2,000 (UL = 3.5) in Santiago Teotlaxco, 1.1/2,000 (UL = 2.6) in Santiago Lalopa, and 0.4/2,000 (UL = 1.2) in La Esperanza. The corresponding seasonal transmission potentials were 2.7, 2.3, and 0.8 third-stage larvae per person, respectively. No evidence for transmission was found in Santa María La Chichina in 2001.[4] Judging from the data reported above, transmission had apparently decreased or ceased in all of these communities by 2004 because infective flies were only detected in La Esperanza in this year.

TABLE 2

Number of persons becoming serologically positive (% of incidence of exposure to onchocerciasis) from 2001 (children ≤ 7 years of age) through 2004 (children ≤ 10 years of age) in four sentinel communities in the focus of Oaxaca, Mexico

Santiago Lalopa	Santiago Teotlaxco	La Esperanza	Santa María La Chichina	Total
0/47 (0%)	0/28 (0%)	0/20 (0%)	0/22 (0%)	0/117 (0%)

When a parasite population is at endemic equilibrium (i.e., before introduction of vector- or ivermectin-based control), the effective reproductive ratio is equal to 1 (regardless of the value of the basic reproduction ratio, which would have been greater than 1 for introduction and persistence of the infection). Once control starts, the parasite population is moved away from this endemic equilibrium and density-dependent constraints are relaxed. This relaxation may make the effective reproductive ratio increase to greater than one initially, but the ratio will decrease in the face of an effective control regimen, eventually becoming less than one. If maintained at this level, the parasite population will eventually become extinct in the area under control. Therefore, what an elimination program such as OEPA wants to achieve is to reduce and maintain the effective reproduction ratio below 1. The reproduction ratio will be determined by the force of infection, which may be measured by the ATP. Unfortunately, the exact relationship between the ATP and the effective reproduction ratio is not known, and the threshold ATP necessary to maintain the reproductive ratio below one is controversial. However, previous deterministic modeling studies using data derived from west Africa and Latin America have suggested that this threshold probably lies somewhere between 5 and 20 third-stage larvae per person per year. All seasonal ATPs in the sentinel villages were within this range in 2004, which suggested that if conditions remain unchanged, the parasite population is likely to be on the path to elimination. The transmission potential in La Esperanza was 6.7 third-stage larvae per year (under endemic unstable equilibrium). In the other communities, the estimated transmission potential was zero. Taking the product of the upper bounds for the 95% CIs for the prevalence of infective flies and the biting rate, the maximal possible transmission potential for La Esperanza is estimated to be 17.2 larvae per person per year, within the 5–20 estimates of previous studies.

It must be emphasized that even when transmission has been suppressed, treatment cannot be discontinued immediately. Transmission may be suppressed by treatment, but it may rebound if the pressure on the population is removed. Thus, it is necessary to maintain control activities until the level of transmission is so low that any rebound in transmission that occurs when control activities end will not reach a level that will cause the reproduction ratio to increase above the breakpoint. Unfortunately, it is difficult to predict to what extent transmission will increase once control activities are ended. This is because the degree of the increase will depend in part upon the competence of the vector, which may in turn

depend upon microfilarial skin densities, with vectors that lack a cibarial armature, such as . . being quite competent at low densities.[10,28,29] Unstable equilibria will also exist because the parasite has separate sexes (e.g., mating probabilities), which again make it difficult to predict with certainty when treatment may be safely stopped. These issues can be explored with relevant stochastic models, which will have to be individually tailored to the ecology of each focus in the Americas.

The serologic data presented above also suggest that transmission may have been brought to undetectable levels throughout much of Oaxaca. However, serologic data do not provide precise estimations of infection rates because some persons exposed to the parasite may develop specific antibodies but never get infected. Thus, detection of circulating antibodies to . . in an exposed population cannot be used to define the presence and level of infection, but these data do have potential utility as an epidemiologic tool to provide an estimate of exposure. In this regard, sampling sentinel cohorts as done here, instead of carrying out mass sampling, could save considerable time, cost, and effort.[30]

The plan for certification of the elimination of onchocerciasis developed by OEPA is made up of four phases.[23] Phase I includes ivermectin treatment for 2–4 years, which results in suppression of transmission. In phase II, suppression is maintained through treatment of the mean reproductive lifespan of the adult female (approximately 13–14 years). After this, (in phase III), it is expected that the adult parasite population would die by senescence and maintaining the suppression of transmission will no longer be dependent on ivermectin distribution. Thus, in phase III, ivermectin distribution will cease and intensive surveillence will be conducted to document that transmission will not re-develop. Finally, in phase IV, the elimination of the . . infection will be certified. The entomologic data presented here show that no evidence for transmission was detected in three sentinel communities of the Oaxaca focus, while that of La Esperanza was apparently below the level currently accepted as the benchmark for transmission suppression by OEPA. Transmission suppression was supported by the serologic data, which showed no evidence for new infections in children in the sentinel communities. More studies are needed in extra-sentinel communities in this focus (i.e., in San Miguel Tiltepec where the first cases of onchocerciasis were discovered in 1924)[31] before we may conclude that transmission of onchocerciasis in Oaxaca has been suppressed throughout the state. Studies of these extra-sentinel communities are currently underway.

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