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AGE-TARGETED CHEMOTHERAPY FOR CONTROL OF URINARY SCHISTOSOMIASIS IN ENDEMIC POPULATIONS

CHARLES H. KING; ERIC M. MUCHIRI/* & JOHN H. OUMA*

Division of Geographic Medicine, Case Western Reserve University School of Medicine Cleveland, Ohio, 44106-4983 U.S.A. *Division of Vector Borne Diseases, Ministry of Health, Nairobi, Kenya

Severity of urinary tract morbidity increases with intensity and duration of Schistosoma haematobium *infection. We assessed the ability of yearly drug therapy to control infection intensity and reduce* S. haematobium*-associated disease in children 5-21 years old in an endemic area of Kenya. In year 1, therapy resulted in reduced prevalence (66% to 22%,* $P < 0.001$*) and intensity of* S. haematobium *infection (20 to 2 eggs/10 mL urine), with corresponding reductions in the prevalence of hematuria (52% to 19%,* $P < 0.001$*). There was not, however, a significant first-year effect on prevalence of urinary tract abnormalities detected by ultrasound. Repeat therapy in years 2 and 3 resulted in significant regression of hydronephrosis and bladder abnormalities (41% to 6% prevalence,* $P < 0.01$*), and further reductions in proteinuria. Repeat age-targeted therapy was associated with decreased prevalence of infection among young children (< 5 yr) entering into the targeted age group. Two years after discontinuation of therapy, intensity of* S. haematobium *infection and ultrasound abnormalities remained suppressed, but hematuria prevalence began to increase (to 33% in 1989). Reinstitution of annual therapy in 1989 and 1990 reversed this trend. We conclude that annual oral therapy provides an effective strategy for control of morbidity due to* S. haematobium *on a population basis, both through regression of disease in treated individuals, and prevention of infection in untreated subjects.*

Key words: *Schistosoma haematobium* – Kenya – control strategies – praziquantel – metrifonate – ultrasound

Human infection with *S. haematobium* carries a high risk for urinary tract injury, which manifests clinically as hematuria, proteinuria, and dysfunction of the ureters and bladder (Warren et al., 1979). In addition, urinary schistosomiasis is associated with significant iron-deficiency anemia (Stephenson et al., 1985a, b), with a predisposition to squamous cell carcinoma of the bladder (Thomas et al., 1990), and with deficits in childhood nutrition and weight gain, as well as deficits in exercise tolerance (Stephenson et al., 1985b, 1989).

Identification of practical means for controlling *S. haematobium*-associated morbidity is a priority for public health workers in endemic areas of Africa. Because of the documented association between intensity of *S. haematobium* infection and many 'acute' forms of morbidity, (e.g., urothelial ulceration and urinary tract granulomata (Abdel-Salam & Ehsan, 1978; Warren et al., 1979; Smith & Christie, 1986; King et al., 1988b), recent non-traditional control strategies have emphasized the goal of reducing worm burden, without necessarily eliminating infection prevalence, in order to limit infection-associated morbidity in populations at risk (Wilkins et al., 1979; Pugh et al., 1980; Stephenson et al., 1984; Mott et al., 1985). Additional evidence from cross-sectional population studies indicates the some forms of 'late' pathology are more prevalent in older individuals, despite their typically lower levels of infection intensity (Smith & Christie, 1986; King et al., 1988b). This suggests that duration of infection is also a significant factor in determining late disease manifestations such as hydronephrosis or bladder cancer. It is likely that the risk for these latter manifestations actually reflects the integral or 'area under the curve' of an individual's age-intensity profile; cumulative injury caused by repeated chronic exposure to *S. haematobium* eggs is likely to result in progressive tissue fibrosis, calcification and malignant transformation.

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Our strategy in designing a control program for schistosomiasis haematobia in Kenya was based on targeting only specific age groups within the endemic communities, i.e., children aged 5-20 years old, for therapy. The rationale was to limit infection intensity in the segment of population known to harbor the highest levels of *S. haematobium* infection, and hence, reduce their risk for 'acute' morbidity, while also treating those infected individuals who would stand to gain the most from limitation of their cumulative exposure to infection. Ecological analysis further predicted that treatment of a sufficient proportion (≥ 75-80%) of the heavily-infected individuals within the community was likely to have a significant impact upon parasite transmission, and could be achieved by targeting school-age children alone (Anderson & May, 1982). In 1984, we began a school-based program for diagnosis and treatment of *S. haematobium* infection in five schools in the Msambweni area of Kwale District, Coast Province, Kenya. This paper summarizes the results of treatment of the prevalence of morbidity and levels of *S. haematobium* transmission in the study communities during the last eight years.

MATERIALS AND METHODS

The design of the Msambweni study has been described in detail in earlier publications (King et al., 1988a, 1990, 1991). Briefly, a 9 village area (1984 population = 8,957), 50 km southwest of Mombasa, was selected for study on the basis of its relative isolation and its high endemicity for *S. haematobium* (50-70%) without *S. mansoni* infection. Residents were identified by house-to-house census. All available school age children were screened for *S. haematobium* infection by Nuclepore filtration technique (Peters et al., 1976), and for the presence of hematuria and/or proteinuria using urine dipsticks (Stephenson et al., 1984). A 1:5 random subsample of those enrolled also received ultrasound examinations of the kidneys and bladder in order to determine the prevalence of hydronephrosis, bladder thickening, calcification, deformity or irregularity (King et al., 1990). Infected individuals were randomized to receive therapy with either metrifonate (Bilarcil, Bayer AG, Leverkusen, Germany), 10 mg/kg for three doses or praziquantel (Biltricide, Bayer) 40 mg/kg as a single dose, followed by two doses of placebo. Followup surveys were performed annually to determine the prevalence and intensity of *S. haematobium* infection, and of hematuria and proteinuria. Followup ultrasound examinations were performed annually (from 1985-1988) on those who had been scanned in the original 1984 survey. In addition, young children entering into the targeted age groups and children immigrating into the area were screened and enrolled into the program in every followup year. Ultrasounds were performed on a 1:5 random sample of these new entrants, and both infected new entrants and newly-infected former participants were randomized to receive either metrifonate or praziquantel therapy in treatment years of the program.

An unusual feature of this study was the continued annual treatment of 1984 entrants for two subsequent years independent of their observed infection status in 1985 and 1986. This approach was taken because the typical level of cure for a single round of therapy is likely to be < 90%, and because sensitivity for diagnosis of very light *S. haematobium* infection (using filtration of a single daily urine sample as was done in this study) may be 85% or less (Warren et al., 1978; Savioli et al., 1990). The basis for giving repeated therapy was to achieve maximal suppression of infection in the community's highest risk age groups (as would be achieved with age targeted-mass therapy independent of parasitological diagnosis) without unnecessarily exposing those children who did not have documented *S. haematobium* infection (at some time point) to antischistosomal medication. Our approach, therefore, was intended to represent a modified form of age-targeted mass chemotherapy.

RESULTS

Participation in the treatment program – During the eight years of the program, a total of 7093 school-age children (5-21 years) from the 5 Msambweni area schools participated in the *S. haematobium* control program. Participation of eligible children, based on periodic village censuses performed by study personnel, was estimated at 91% in 1984, 71% in 1985, 68% in 1986, 56% in 1987, 71% in 1988, 40% in 1989 (in an intentionally limited survey), 74% in 1990, and 74% in 1991. Participation was typically highest in the 12-15 age group (74-93%) each year, and lowest in the over 19 age group (24-58%). Followup of previously enrolled students ranged from 55-76% after their first year of participation, from 39-59% after the second year, and from 47-

56% after the third year. After seven years, participation of 1984 entrants was 23%. In general, each annual survey represents a cross-section of the school-age population of the Msambweni area. Interpretation of treatment outcomes must be tempered by loss to followup in each subsequent year.

Impact of repeated annual treatment on prevalence and intensity of S. haematobium *infection* – Fig. 1 details the impact of therapy given in 1984, 1985, 1986, 1989, and 1990 on the prevalence and intensity of *S. haematobium* infection in the different Msambweni age groups participating in the study. It also shows the prevalence and intensity of infection in the untreated adults surveyed each year. Overall, there were significant reduction in *S. haematobium* prevalence in the school-age groups after each of the first two rounds of treatment. Prevalence among children fell from 66% before therapy, to 22% in 1985 ($P < 0.001$), and to 15% in 1986 ($P < 0.001$ versus 1984 and 1985). By contrast, prevalence among surveyed adult villagers remained steady at 31% in 1984, 30% in 1985, and 30% in 1986 (NS). Therapy was

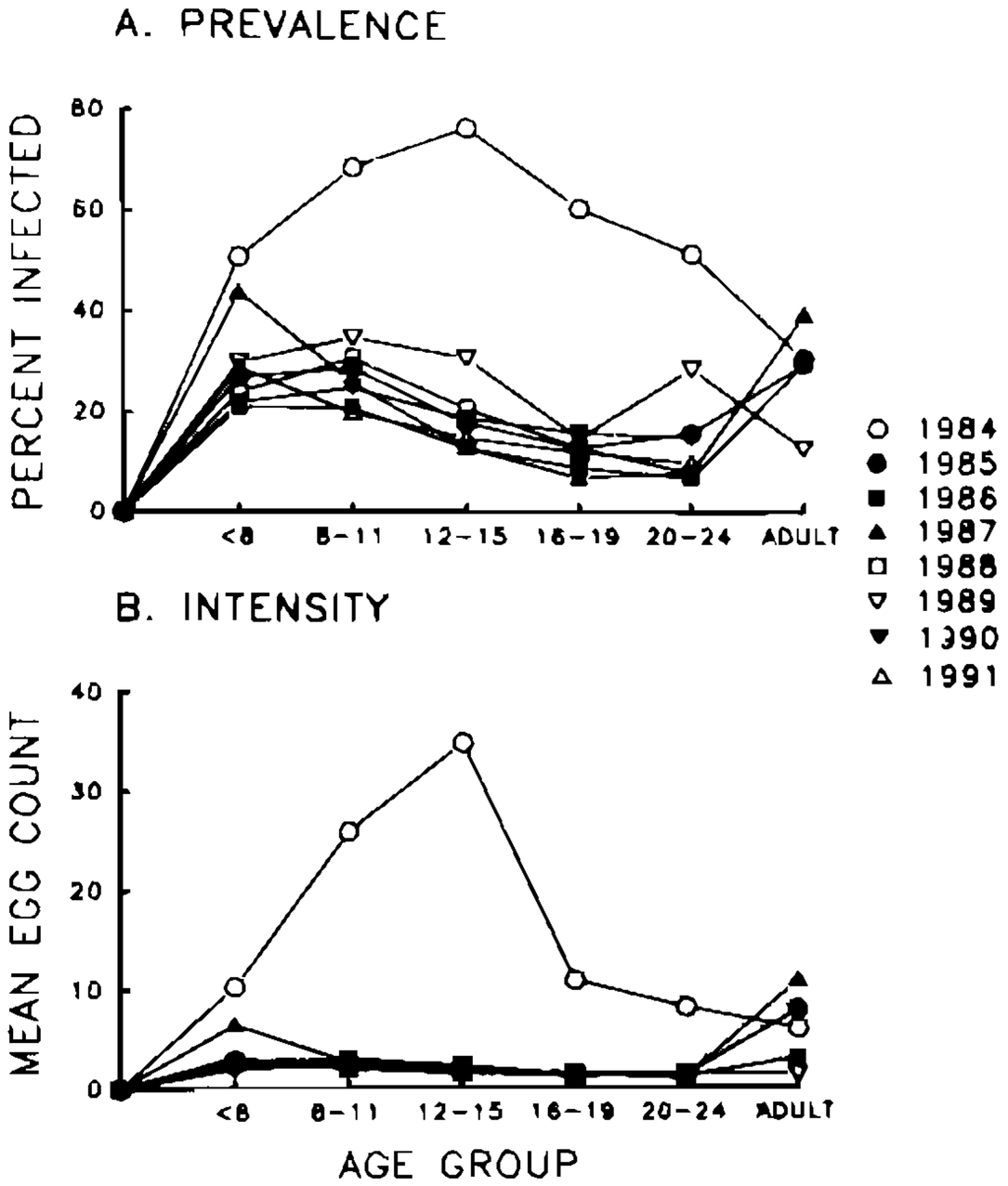

Fig. 1: age-prevalence (panel A) and age-intensity (panel B) profiles for *Schistosoma haematobium* infection in the 9 Msambweni study villages during the period 1984-1991. Drug treatment was administered to school-age children (5-21) in 1984, 1985, 1986, 1989, and 1990.

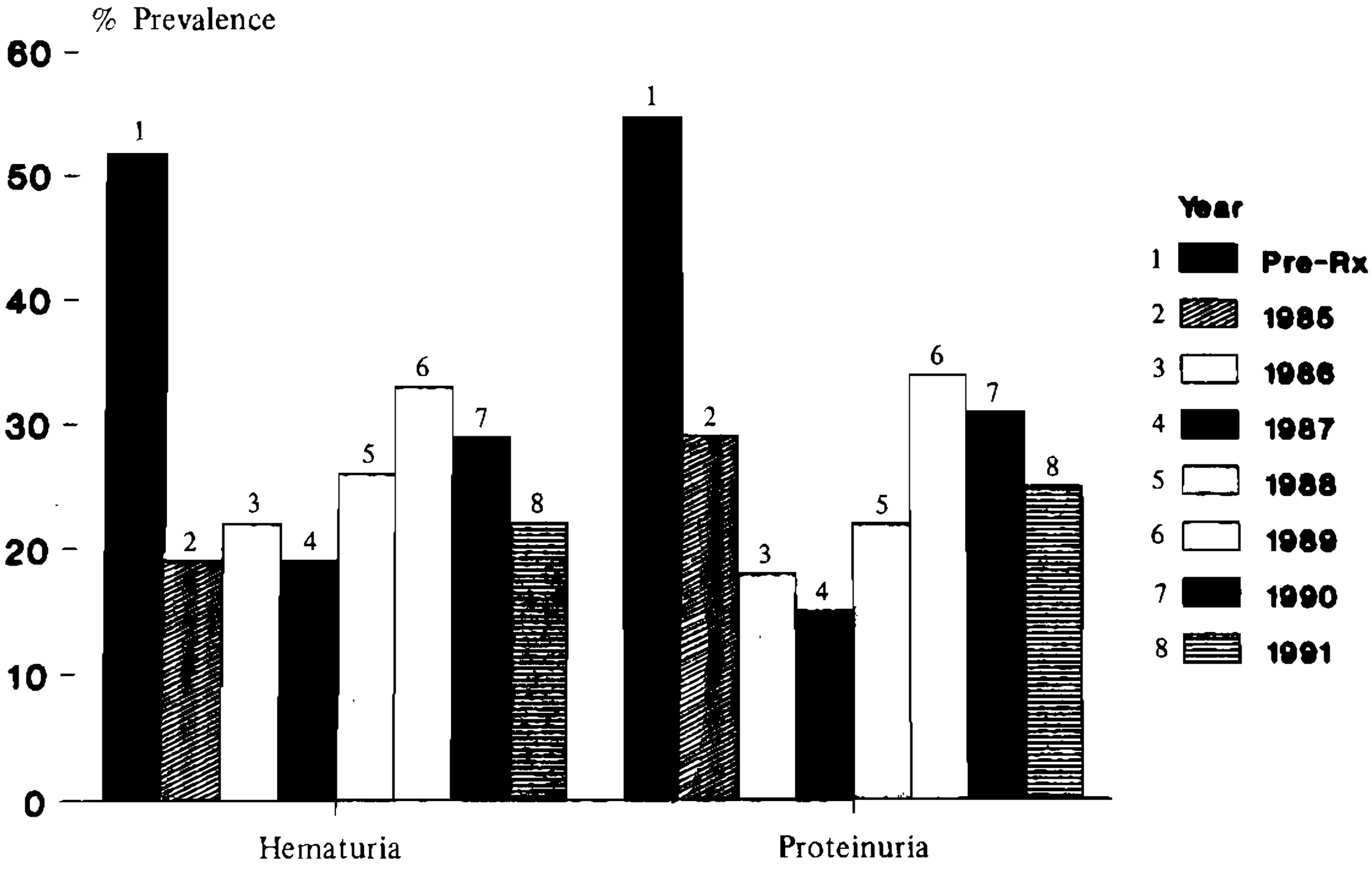

Fig. 2: prevalence of dipstick hematuria and proteinuria among school age children (5-21 years) in the Msambweni study area during the period 1984-1991.

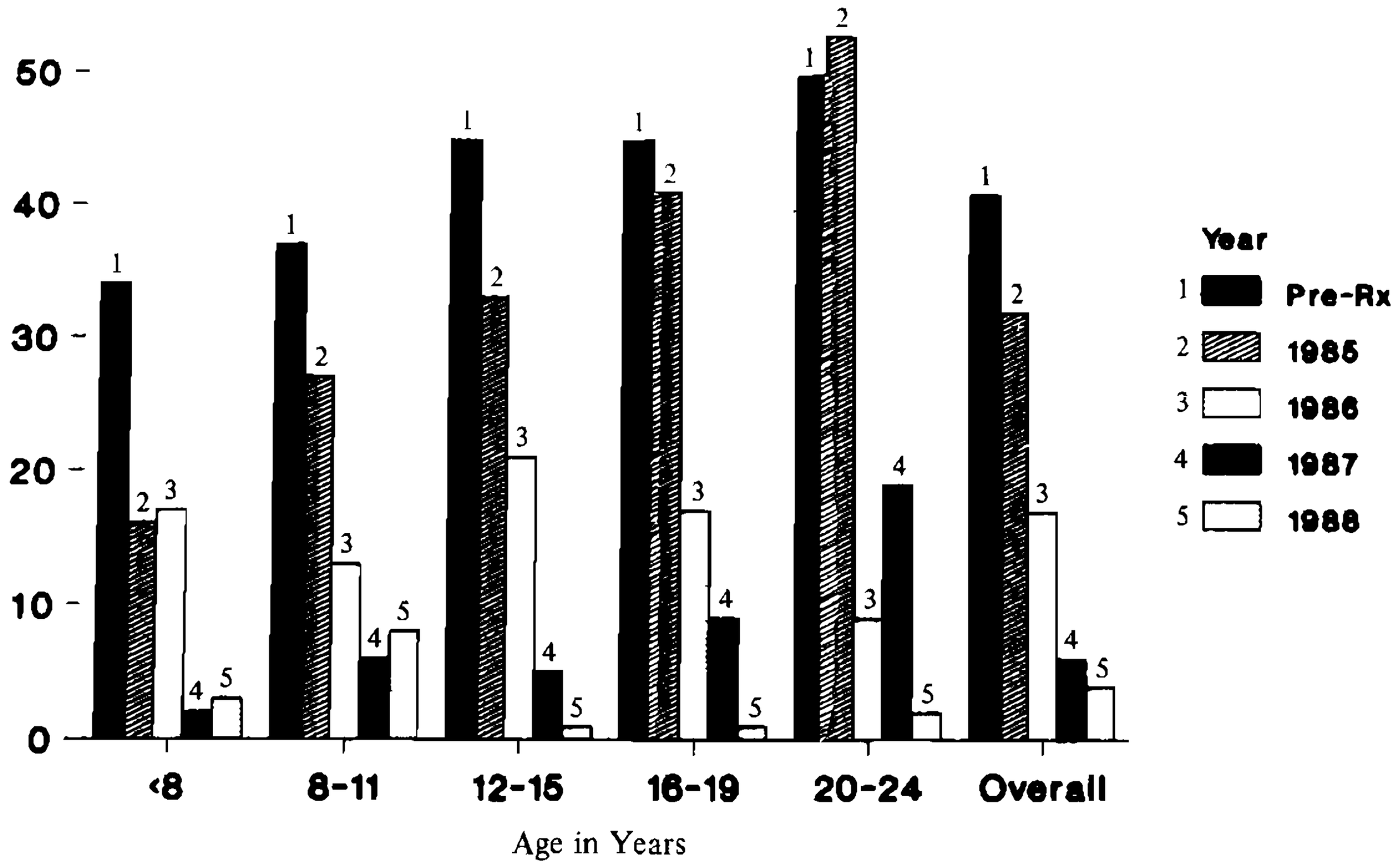

Fig. 3: prevalence of ultrasound abnormalities (hydronephrosis, bladder irregularity or bladder thickening) in the targeted age groups during the period 1984-1988.

suspended for most participants in 1987 and 1988, resulting in a gradual increase in school age prevalence to 30% in 1989 ($P < 0.001$). Therapy (for infected children only) was resumed at that point, with subsequent reduction in prevalence to 21% in 1990 and 17% in 1991 ($P < 0.001$ for both years versus 1989). Geometric mean intensity of infection was 20 eggs/10 mL urine prior to the institution of therapy in 1984. Following treatment, mean intensity of infection dropped to 2 eggs/10 mL, and remained suppressed at this level throughout the 1985-1991 period.

Impact of therapy on prevalence of morbidity – Fig. 2 details the impact of therapy on the prevalence of hematuria and proteinuria in the school-age population studied. Hematuria prevalence was reduced after the first year of treatment, and remained suppressed at < 25% through 1987. Hematuria prevalence began to increase after suspension of therapy in 1987, reaching 33% by 1989 ($P < 0.001$ versus 1985). Following reinstitution of therapy that year, hematuria prevalence again fell, reducing to 22% by 1991 ($P < 0.001$ versus 1989). Proteinuria prevalence took two years to reach maximal suppression, declining from 56% before therapy to 29% in 1985 and 18% in 1986 ($P < 0.001$ for both 1985 and 1986 versus 1984). Prevalence of proteinuria among the school age population increased within one year of suspension of widespread therapy in 1987 (to 22% in 1988 and 34% in 1989 ($P < 0.001$ compared to 1986)), but fell again following the reinstitution of treatment in 1989 (1991 proteinuria prevalence was 25% ($P < 0.001$ versus 1989)).

Following the introduction of therapy in 1984, there was significant reduction in the prevalence of urinary tract lesions detected on ultrasound (Fig. 3). The youngest three age groups showed significant reduction in prevalence of urinary tract of abnormalities within one year ($P < 0.05$), while among older individuals, there was no significant first-year effect on ultrasound abnormalities.

To determine if established hydronephrosis could regress following curative therapy, we did a case-control analysis of the twenty 1984 entrants who had moderate or severe hydronephrosis scores on their ultrasound examinations. Fig. 4 indicates that in serial annual followup, these individual's mean hydrone-

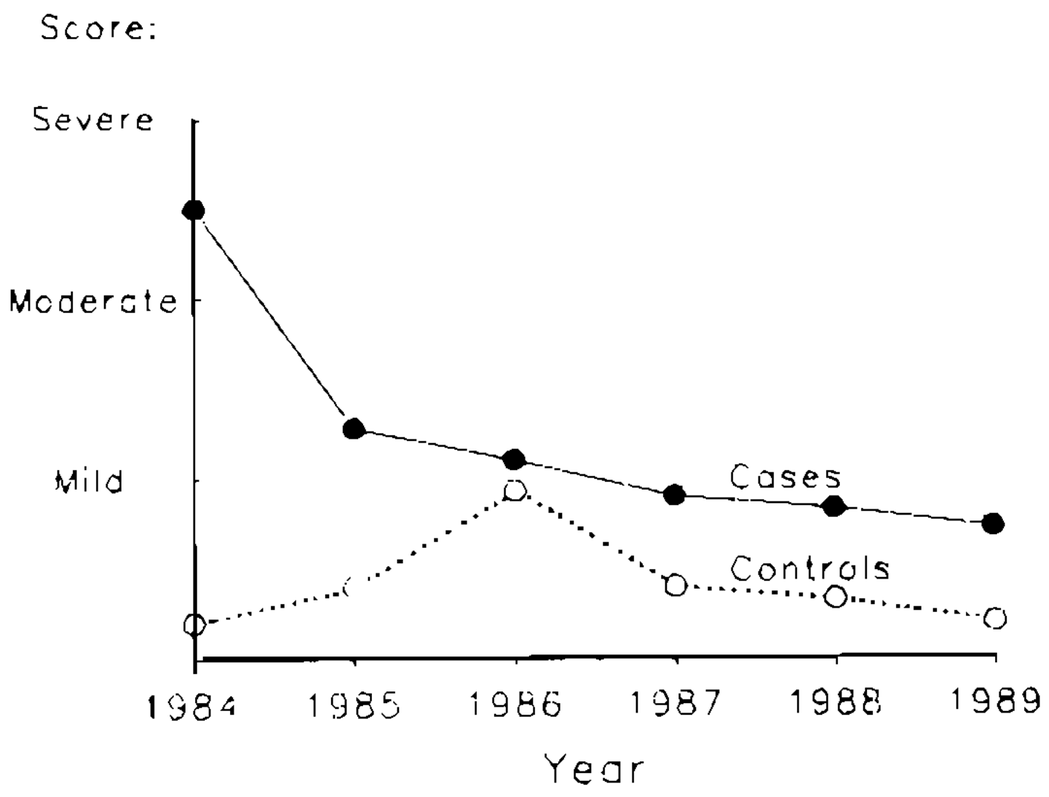

Fig. 4: mean hydronephrosis scores for 20 individuals with moderate or severe hydronephrosis in 1984 (filled circles) in subsequent followup 1985-1989. Also shown are the average scores of 20 age-, sex-, and infection intensity-matched controls from the same area (hollow circles). One year after institution of therapy in 1984, the group of affected individuals showed a significant decrease in average hydronephrosis score, which remained suppressed throughout the observation period.

phrosis scores declined significantly ($P < 0.005$), while the scores of twenty unaffected age-, sex-, and *S. haematobium* infection intensity-matched controls were not significantly different from their starting scores. In closer analysis, the apparent persistence of ureteral abnormalities in older age groups was associated with progression of hydronephrosis scores in some individuals, particularly males over 12 years old, despite effective eradication of their *S. haematobium* infection (King et al., 1990). This progression of disease in some individuals during 1984-1985 counterbalanced improvement in other individuals, leading to no net improvement in the older age groups. After 1985, all age groups showed continued reduction in the prevalence of urinary tract abnormalities, such that prevalence was only 6% for any abnormality in 1988, and severe hydronephrosis was not detected in any ultrasound examination. In 1988, an expanded ultrasound survey of 158 new study entrants aged 5-19 revealed that these previously untreated individuals (who had nevertheless resided in the control area for ≥ 4 years) had a profile of urinary tract morbidity that was less severe than the untreated entry group studied in 1984. Severe hydronephrosis in the untreated 1988 entrants was absent, moderate hydronephrosis was reduced from 2.4% (in 1984) to 1.3% (in 1988), and bladder abnormalities were reduced from 39% to 11% ($P < 0.001$).

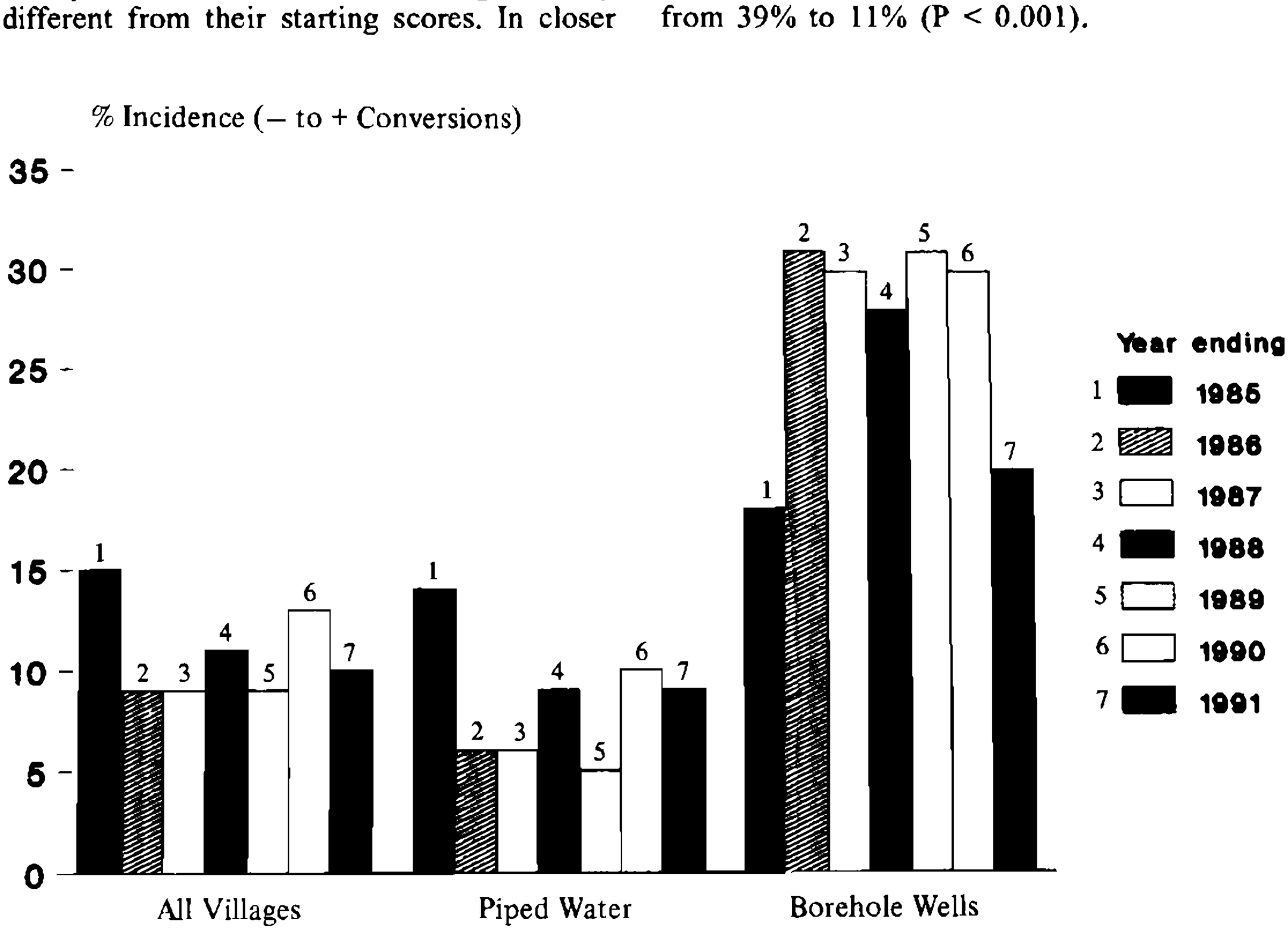

Fig. 5: incidence of *Schistosoma haematobium* infection estimated as negative-to-positive conversion on urine filtration testing for parasite eggs. Overall the rate of conversion was significantly lower after the second year of therapy, suggesting a lowering of overall transmission rates. Conversion rates remained high in villages without access to piped water, suggesting that transmission was not affected in those areas.

Impact of therapy on transmission – To gauge the effects of targeted therapy on community levels of *S. haematobium* transmission, we evaluated incidence of *S. haematobium* infection (measured as negative-to-positive conversion on egg counts) and monitored levels of infection in young children entering into the program for the first time each year. Fig. 5 details the rate for egg count conversions for the seven yearly intervals of the study. Overall, there was a clearcut decline in such conversions by 1986 ($P < 0.001$), and this effect was particularly marked in those villages having access to piped water. No significant decline was noted in villages having access only to surface water sources or to borehole wells, suggesting that transmission was not affected in those areas. Control studies, employing direct observations of water contact activities on a rotating, randomized schedule, indicated no significant changes in water contact frequency or mean duration in either group of villages during the course of the study (El Kholy et al., 1989). Analysis of infection levels in new entrants indicated reduced infection in this 'sentinel' group in every year after the introduction of therapy (King et al., 1991). As with the egg count conversion data, this reduction was significant in villages with piped water but was not observed in the villages having only well or surface water access.

DISCUSSION

These findings indicate that a school-based program of chemotherapy for *S. haematobium* infection can have significant effects in suppressing infection prevalence and infection intensity, with consequent reductions in the prevalence of hematuria, proteinuria and structural urinary tract abnormalities. Benefits accurued not only to those treated, who showed regression of morbidity findings in all categories after the second year, but also to those who were not treated. This latter effect was manifested by reductions in new infections, by reductions in infection prevalence among untreated young children, and by reduced levels of severe ultrasound abnormalities in children entering school for the first time. Some of these beneficial effects were not seen in high-risk villages. These had initially very high prevalence of *S. haematobium* infection, high levels of infection prevalence among adults, and no access to piped water (El kholy, et al., 1989). It is evident that additional control measures, including therapy of adult populations, will be necessary to control transmission in those areas (King et al., 1991).

Our data are limited by the lesser sensitivity of urine filtration for very light infections, which are most common after therapy (Warren et al., 1978; Savioli et al., 1990). This effect would lead to underestimation of the true level of infection prevalence, possibly by up to 20% in post-therapy years. However, this phenomenon would have only a minimal impact on calculation of mean egg counts, and the observed therapeutic effects on community mean infection intensity are likely to be close to actual values. The data are also limited by a 20-50% loss to followup of participants in annual surveys. It may be that these individuals represent a high risk group who continue to carry infection, and who may manifest relatively high levels of *S. haematobium*-associated morbidity, leading to an overestimation of therapeutic effects on our part. Yearly analysis of the demographic features of individuals leaving the program indicates that they are primarily older children who leave school to seek employment or to attend secondary school in other areas. Periodic village surveys of absentees from the program indicate that missing older individuals do not harbor more infection than their screening-compliant, but therapy non-compliant, age-group peers. We find that assigning missing individuals their last known infection status, or their age-group peers' mean data scores, does not influence the interpretation of the data in terms of therapeutic suppression of morbidity.

The results of the first year of therapy, in terms of screening and therapeutic compliance, mimicked levels of compliance and efficacy that would have been achieved if we had chosen to use age-targeted mass therapy (without relying on parasitologic diagnosis) to assign treatment, as recommended by some experts for areas of high endemicity (Anderson & May, 1982). Evidently, such an approach would have effected significant reductions in morbidity and in *S. haematobium* transmission as well.

We have recently initiated a program of formal decision analysis (based on our results) to determine the factors involved in providing optimal suppression of disease in situations with limited monetary resources. Our preliminary findings, using historical cost data, indicate that mass therapy is most appropriate to communities with prevalence > 70%, while in

communities having prevalence in the range of 45-70%, reagent dipstick diagnosis of hematuria (as a surrogate for infection), may be the most cost-effective means of determining treatment assignment. Our ongoing studies in the area of operational research are focusing on how best to apply the finding of this pilot program to larger populations (> 200,000). This will involve refinement and field testing of the predictions of decision analysis, the streamlining of sampling methods to estimate village prevalence, and the development of spreadsheet programs to determine strategies in the field and perform quality control. These innovations are now being tested as part of the implementation of a National Schistosomiasis Control Program in Kenya, under the auspices of the Division of Vector Borne Diseases of the Ministry of Health.

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