Tuberculosis and the HIV Epidemic: Increasing Annual Risk of Tuberculous Infection in Kenya, 1986–1996

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ABSTRACT

Objectives. The purpose of this study was to assess the impact of the increased incidence of tuberculosis (TB) due to HIV infection on the risk of TB infection in schoolchildren.

Methods. Tuberculin surveys were carried out in randomly selected primary schools in 12 districts in Kenya during 1986 through 1990 and 1994 through 1996. Districts were grouped according to the year in which TB notification rates started to increase. HIV prevalence in TB patients and changes in TB infection prevalence were compared between districts.

Results. Tuberculous infection prevalence rates increased strongly in districts where TB notification rates had increased before 1994 (odds ratio = 3.1, 95% confidence interval = 2.3, 4.1) but did not increase in districts where notification rates had increased more recently or not at all. HIV prevalence rates in TB patients were 50% in districts with an early increase in notification rates and 28% in the other study districts.

Conclusions. Countries with an increasing prevalence of HIV infection will need additional resources for TB control, not only for current patients but also for the patients in additional cases arising from the increased risk of TB infection. (*Am J Public Health.* 1999;89:1078–1082)

In individuals infected with *Myobacterium tuberculosis,* the risk of developing tuberculosis (TB) increases in those also infected with HIV.[1–4] In various countries with a high prevalence of HIV infection, TB notification rates have increased.[4,5] It is unclear whether this increase is the result of an increased risk of TB infection in individuals without HIV infection.

Kenya has a high prevalence of HIV infection. As of November 1996, 69 005 AIDS cases had been reported to the Ministry of Health.[6] Kenya has had a national TB control program since 1958. Between 1958 and the period from 1986 through 1990, the annual risk of TB infection declined by 75% (from 2.5% to 0.6%), approximately 4.6% annually.[7] National tuberculin surveys were carried out in 1986 through 1990 and in 1994 through 1996. In this article, we report trends in annual risk of TB infection and their association with TB case notification rates and HIV infection prevalence.

Methods

The 1986–1990 tuberculin survey was carried out in 12 districts representing the locations included in a 1958 survey.[7,8] Within districts, schools were sampled via probability-proportional-to-size methods.[7,9] The 1994–1996 survey was carried out in the same districts and the same schools. Readers of Mantoux skin-test indurations (2 in the first survey, 4 in the second) were trained by the same reference nurse. Agreement between trainer and readers was good (weighted kappa values were 0.9 or higher for all readers with the allowance of 2-mm differences). The survey was approved by the ethical committee of the Kenya Medical Research Institute and the director of education of Kenya.

On the day of the survey, a list of children in grades 1 through 3 was prepared. Age, sex, and the presence of a BCG vaccination scar were recorded. A 1-mL disposable syringe and a disposable 26-gauge needle were used in administering 2 TU purified protein derivative (PPD) RT-23 with Tween on the dorsal side of the right forearm. Reactions to the Mantoux test were read 3 days later (with a ruler) as the maximum transverse diameter of the induration.[10,11]

In calculating district prevalences of TB infection, we assigned equal weights to the prevalences of infection among non–BCG-vaccinated children in each school.[12] Similarly, in estimating the national prevalence, we assigned equal weights to each district prevalence. The confidence interval (CI) of the national prevalence was based on the variation among districts.[13] As in the earlier survey, infection prevalence was estimated by the number of reactions of 17 mm in addition to twice the number of larger reactions.[7,14,15] We explored alternative cutoff points in the range of 10 mm to 25 mm for a "positive" PPD to estimate trends.[16]

We used the formula $1-(1-\text{Prevalence})^{1/\text{mean age}}$ to calculate the annual risk of

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TABLE 1—Study Population, BCG Vaccination Status, Tuberculous Infection Prevalence, and Annual Risk of Infection: Kenya, 1994–1996

District	No. Enrolled	Tested and Read,[a] No. (%)	Non–BCG Vaccinated,[b] No. (%)	Tuberculous Infection Prevalence, %	Mean Age, y	Annual Risk of Infection (95% Confidence Interval)
Kisii	4529	3796 (84)	538 (14)	6.3	8.8	0.7 (0.3, 1.2)
South Nyanza–Homa Bay	3927	3354 (85)	654 (19)	12.2	9.6	1.3 (0.8, 1.9)
Kakamega	5107	4447 (87)	667 (15)	8.9	8.9	1.0 (0.5, 1.6)
Siaya	4560	3741 (82)	546 (15)	9.8	9.0	1.1 (0.6, 1.7)
Nairobi	4637	4205 (91)	389 (9)	20.9	8.0	2.9 (1.9, 4.0)
Nakuru	4993	4511 (90)	411 (9)	5.1	8.4	0.6 (0.2, 1.1)
Muranga	4975	4420 (89)	330 (7)	5.7	8.3	0.7 (0.1, 1.3)
Kitui	4373	3558 (81)	395 (11)	10.2	9.6	1.1 (0.5, 1.7)
Elgeyo Marakwet	3764	3255 (86)	276 (8)	15.3	8.9	1.9 (0.6, 3.3)
Meru	4345	3997 (92)	485 (12)	4.1	9.6	0.4 (0.1, 0.8)
Kilifi	6090	4846 (80)	1525 (31)	6.7	9.4	0.7 (0.5, 1.0)
Kwale	5139	4492 (87)	1340 (30)	8.6	9.7	0.9 (0.6, 1.2)
Total	56439	48622 (86)	7556 (16)	9.5	9.0	1.1 (0.8, 1.4)

[a]Among children aged 6–14 years.
[b]In calculations, equal weights were given to the prevalences at each school.

TB infection, the fraction of the population that is infected (or reinfected) during a calendar year.[17,18]

Numbers of new smear-positive TB cases were obtained from the National Leprosy and Tuberculosis Control Programme, which applied a uniform notification system over the study period. Population data were based on the 1989 census and the district-specific intercensus growth rate from 1979 through 1989.[19] District-specific HIV prevalence rates in TB patients were obtained from a survey conducted in 1993–1994, in which 1135 consecutive new smear-positive TB patients were tested for HIV in the study districts (J. van Gorkom et al., unpublished data, 1997).

We examined the association between changes in TB notification rates and the annual risk of TB infection by comparing 3 groups of districts. In group 1, notification rates of smear-positive TB began to increase before 1994 (i.e., before the survey); in group 2, notification rates increased from 1994 through 1996; and in group 3, notification rates did not increase.

The start of the increase was defined as the first year in which the notification rate was at least 30% higher than the average during 1986–1989. Odds ratios (ORs) of infection in the 2 surveys were adjusted via logistic regression analyses involving age, sex, and district; schools were used as the clusters of observation.

Results

During 1994–1996, 56439 children were tested; 48622 (86%) of the children were aged 6 to 14 years, classified by BCG status, and present when indurations were read (Table 1). Of these 48622 children, 7556 (mean age: 9.0 years) had no BCG scar and were included in analyses. Their distribution of indurations is presented in Figure 1. The prevalence of TB infection in these children was estimated at 9.5% (95% CI = 6.6%, 12.3%), corresponding to an annual risk of TB infection of 1.1% (95% CI = 0.8%, 1.4%) (Table 1). The annual risk of TB infection was higher during 1994–1996 than during 1986–1990 (OR = 1.4, 95% CI = 1.2, 1.7) (Table 2). The difference between the surveys was little affected by the cutoff point for a "positive" PPD, with crude odds ratios for different cutoff points varying between 1.5 and 1.8. There was no association between the size of the induration used as the cutoff point and the odds ratio ($r = -0.093$, $P > .05$).

Notification rates of smear-positive TB increased strongly in group 1 districts and moderately in group 2 districts; no increases were seen in group 3 districts (see Figure 2A). Group 1 included districts in western Kenya and Nairobi, group 2 was situated in central Kenya, and group 3 was situated in eastern Kenya (Figure 2B). As shown in Table 2, there was a marked increase in TB infection prevalence in group 1 districts (OR = 3.1, 95% CI = 2.3, 4.1), no significant increase in group 2 districts (OR = 1.1, 95% CI = 0.8, 1.5), and a small decrease in group 3 districts (OR = 0.7, 95% CI = 0.5, 1.0).

In 1994, HIV prevalence rates among TB patients in district groups 1, 2, and 3 were 50%, 29%, and 27%, respectively ($c^2 = 23.1$, $P < .0001$) (Table 2). The corresponding BCG vaccination coverage rates were 85%, 90%, and 69% (Table 1). BCG coverage increased between the 2 surveys in all districts. The increase was highest in group 2 (OR = 5.0), somewhat lower in group 1 (OR = 3.6), and lowest in group 3 (OR = 1.9).

Discussion

This study shows that the annual risk of TB infection in Kenya has increased in the past decade. The largest increase occurred in districts where TB notification rates had risen before 1994; these districts also had high HIV prevalence rates among both TB patients and patients attending antenatal clinics (Kenya National AIDS Control Programme, unpublished data, 1998; also available at: http://www.who.int/emc-hiv/fact_sheets/africa.html). This is the first documentation of an increased annual risk of TB infection in young schoolchildren associated with rising TB incidence rates in areas with a high prevalence of HIV.

HIV infection strongly increases the risk of developing smear-positive TB.[1–3] Although the infection prevalence may be somewhat lower in smear-positive TB patients with HIV than in smear-positive patients without HIV,[20–22] the marked increase in TB incidence in individuals with HIV apparently is not offset by this decrease in infectiousness.

During most of the period of exposure to TB infection of the children included in the survey, "standard" chemotherapy was used in Kenya, comprising 18 months of isoniazid and thiacetazone (in the first month, in combination with streptomycin). During 1993–1995, short-course chemotherapy was

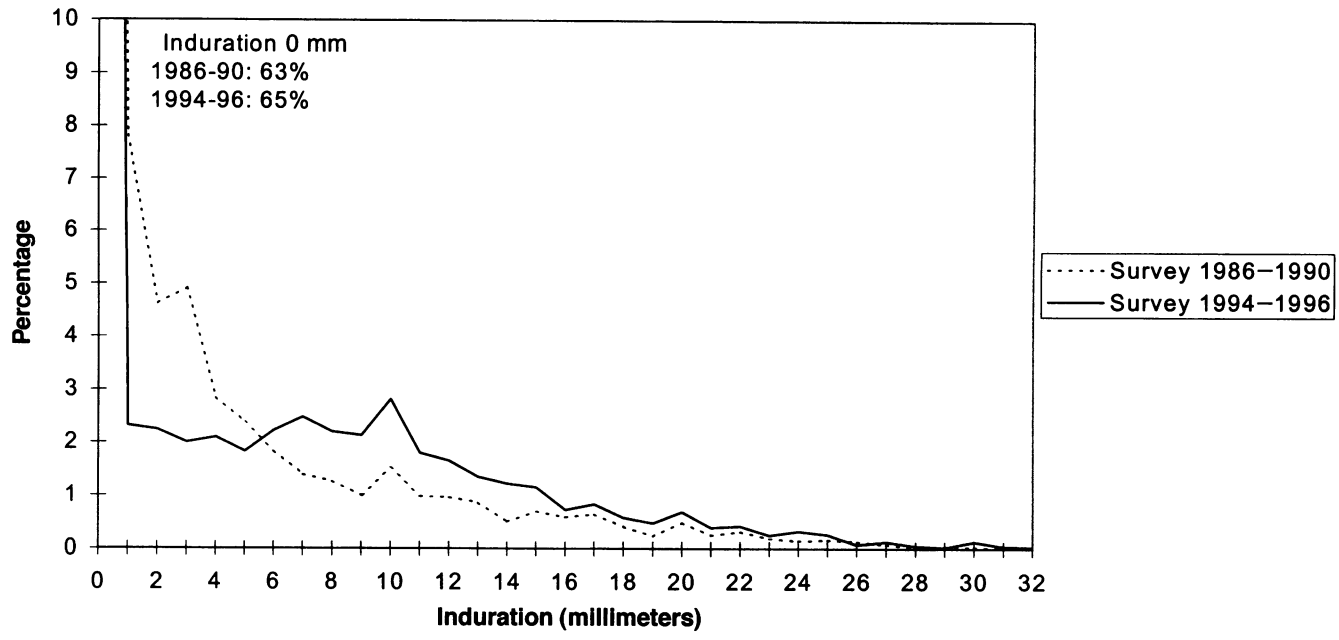

FIGURE 1—Frequency distributions of indurations in reaction to 2 TU purified protein derivative RT-23 in non–BCG-vaccinated schoolchildren: Kenya, 1986–1990 and 1994–1996.

introduced, consisting of 2 months of rifampicin, isoniazid, pyrazinamide, and streptomycin, followed by 6 months of isoniazid with either thiacetazone or ethambutol. Thus, this study does not directly address the question of the extent to which increased transmission of TB due to HIV infection can be contained by a well-established directly observed therapy short-course program. It is possible that a more limited increase in the risk of TB infection would be observed in countries where rifampicin-containing short-course regimens were introduced earlier; these regimens have cure rates on the order of 85%, as opposed to the 65% rate associated with "standard" therapy.[23,24]

In this study, schoolchildren were not tested for HIV, an infection that may cause anergy and thereby lead to underestimation of increases in annual risks of TB infection.

TABLE 2—Trends in Tuberculous (TB) Infection Prevalence in 3 District Groups in Kenya, Defined by Year in Which Notification Rates Increased by More Than 30% vs the Period 1986–1989

District and Trend	HIV Prevalence Among TB Patients, 1993–1994, %	Initial Year of Notification Rate Increase	Prevalence of Infection		Crude Odds Ratio[b]	Adjusted Odds Ratio[c] (95% Confidence Interval)
			1986–1990, No. Positive[a] (%)	1994–1996, No. Positive[a] (%)		
1. Early increase (1990–1993)	50	...	241 (3.7)	315 (11.3)	3.3	3.1 (2.3, 4.1)
Kisii	26	1990	46 (3.2)	38 (7.1)	2.3	2.4 (1.3, 4.1)
South Nyanza–Homa Bay	73	1991	50 (4.0)	77 (11.8)	3.2	2.7 (1.5, 4.6)
Kakamega	33	1991	47 (3.3)	49 (7.3)	2.4	2.8 (1.4, 5.8)
Siaya	80	1992	44 (2.9)	54 (9.9)	3.7	3.7 (1.9, 7.5)
Nairobi	36	1993	54 (6.9)	97 (24.9)	4.5	4.0 (2.2, 7.2)
2. Late increase (1994–1996)	29	...	364 (5.9)	130 (6.9)	1.2	1.1 (0.8, 1.5)
Nakuru	41	1994	65 (4.7)	21 (5.1)	1.1	1.2 (0.5, 2.9)
Muranga	21	1994	16 (1.2)	16 (4.8)	4.2	4.3 (1.7, 11)
Kitui	34	1995	146 (11.7)	39 (9.9)	0.8	0.8 (0.4, 1.4)
Elgeyo Marakwet	...	1995	51 (5.4)	32 (11.6)	2.3	1.8 (0.9, 3.7)
Meru	20	1996	86 (6.9)	22 (4.5)	0.6	0.6 (0.3, 1.2)
3. No increase	27	...	248 (10.1)	213 (7.4)	0.7	0.7 (0.5, 1.0)
Kilifi	24	...	176 (13.8)	106 (7.0)	0.5	0.5 (0.3, 0.7)
Kwale	29	...	72 (6.1)	107 (8.0)	1.3	1.3 (0.8, 2.1)
Total	36	...	853 (5.7)	658 (8.7)	1.6	1.4 (1.2, 1.7)

[a]Calculated as number with an induration of 17 mm plus 2 times the number with an induration of 18 mm or more.
[b]Calculated via the numbers of children positive and negative.
[c]Calculated via comparisons of all indurations of 17 mm or more and adjusted for age, sex, and district, taking schools as clusters of observations and using generalized estimating equations. All odds ratios compared the odds in 1994–1996 with the odds in 1986–1990.

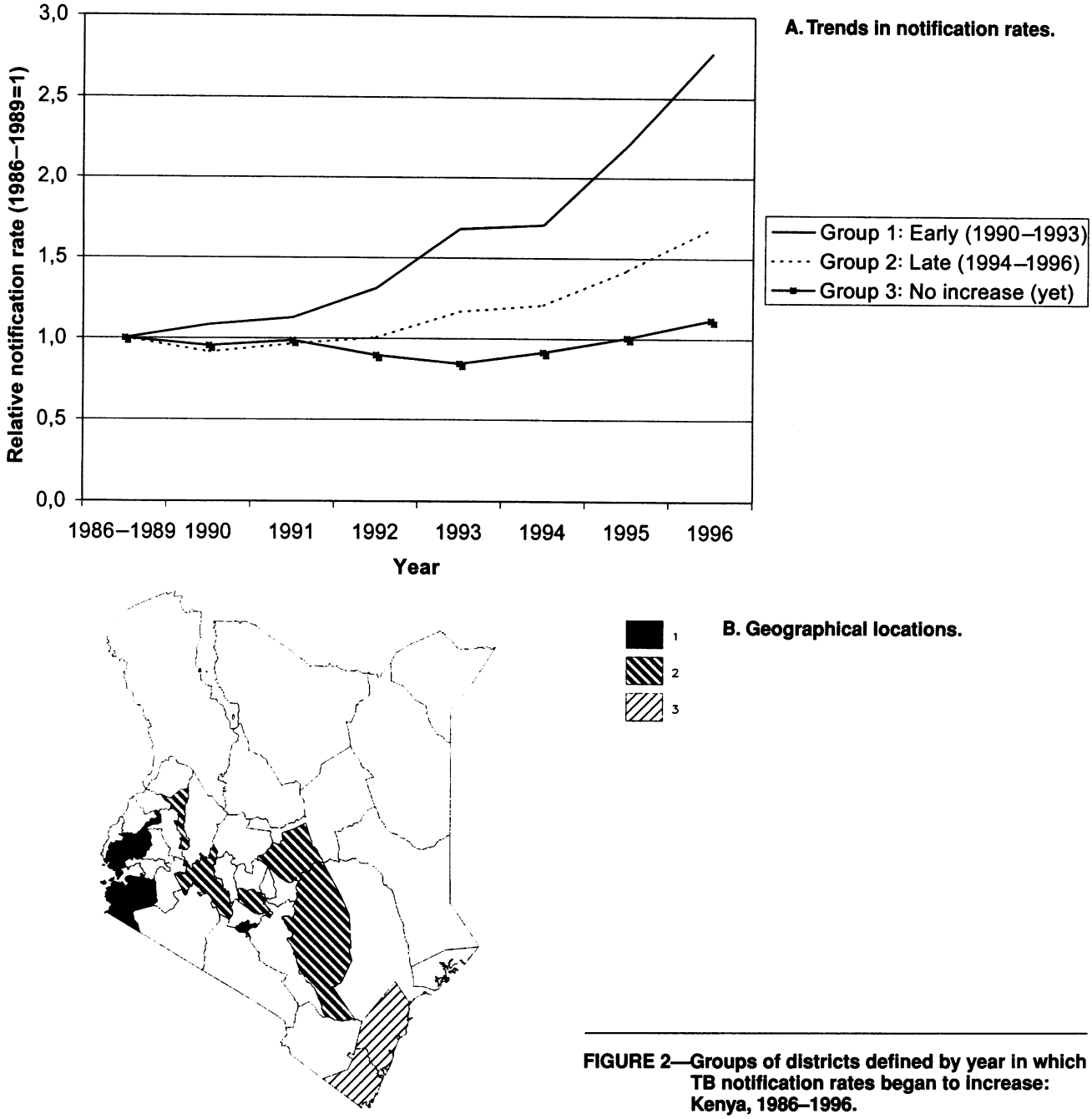

FIGURE 2—Groups of districts defined by year in which TB notification rates began to increase: Kenya, 1986–1996.

However, HIV prevalence is probably very low in this age group and is unlikely to have influenced the results. In 1995, treatment completion rates in district groups 1, 2, and 3 were 66%, 74%, and 62%, respectively. Differences in cure rates do not explain the observed results. Although increased notification rates were observed in group 2 districts after 1994, the annual risk of TB infection had not (yet) increased. As measured during 1994–1996, this annual risk represents an average lifetime risk for schoolchildren. Although the risk probably increased from 1994 through 1996 in group 2 districts, its influence on the average lifetime risk among 7-year-olds (as measured during 1994–1996) should be very limited.

The results in Muranga District differed from those in other districts: no increased TB notification rates were found, but a significant increase in the prevalence of TB infection was noted. Perhaps, as suggested in the report on the first survey,[7] this is the result of underestimation of TB infection prevalences in that survey in Muranga owing to measurement problems. Because Muranga was not in group 1, this finding cannot invalidate our conclusion that increased TB rates accounted for the increased infection prevalence in group 1 districts.

BCG vaccination coverage increased considerably between the 2 surveys. Non–BCG-vaccinated individuals may have become increasingly unrepresentative of the general population, and an increasing proportion of those categorized as not having a BCG scar may have been misclassified.[16,25] The latter would have little impact on our results; the odds ratios in groups 1, 2, and 3 among BCG-vaccinated children were 2.2, 1.1, and 0.7, respectively. Moreover, BCG vaccination coverage and its increase between the surveys

were highest in the districts of group 2, where no increase was observed in TB infection prevalence.

In conclusion, countries with increasing HIV prevalence rates may face an increasing TB problem in individuals both with and without HIV infection. Thus, additional resources for TB control are needed for the currently increased number of patients as well as for patients in the additional cases arising from the increased risk of TB infection. □

Contributors

J. A. Odhiambo was the principal investigator and conducted the design and analysis of the study and the writing and finalization of the paper. M. W. Borgdorff designed and conducted the data analysis and participated in the writing of the paper. F. M. Kiambih, K. K. Kibuga, D. O. Kwamanga, and R. Agwanda participated in the design and implementation of the tuberculin surveys. L. Ng'ang'a and N. A. Kalisvaart were responsible for data management and initial data analysis. O. Misljenovic participated in the study design and the training of the survey team. N. J. D. Nagelkerke participated in data analysis and finalization of the paper. M. Bosman participated in study design, supervision of data collection, and finalization of the paper.

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References

1. Harries AD. Tuberculosis and human immunodeficiency virus infection in developing countries. *Lancet.* 1990;335:387–390.
2. Perriens JH, Mukadi Y, Nunn P. Tuberculosis and HIV infection: implications for Africa. *AIDS.* 1991;43(suppl):S127–S133.
3. De Cock KM, Soro B, Coulibaly IM, Lucas SB. Tuberculosis and HIV infection in sub-Saharan Africa. *JAMA.* 1992;268:1581–1587.
4. De Cock KM, Binkin NJ, Zuber PL, Tappero JW, Castro KG. Research issues involving HIV-associated tuberculosis in resource-poor countries. *JAMA.* 1996;276:1502–1507.
5. Cantwell MF, Binkin NJ. Tuberculosis in sub-Saharan Africa: a regional assessment of the impact of the human immunodeficiency virus and National Tuberculosis Control Program quality. *Tuberc Lung Dis.* 1996;77:220–225.
6. World Health Organization. Global AIDS surveillance. *Wkly Epidemiol Rec.* 1997;72: 197–200.
7. Bosman MCJ, Swai OB, Kwamanga DO, Agwanda R, Idukitta G, Misljenovic O. National tuberculin survey of Kenya 1986–1990. *Int J Tuberc Lung Dis.* 1998;2:272–280.
8. Roelsgaard E, Nyboe J. A tuberculosis survey in Kenya. *Bull World Health Organ.* 1961;25: 851–870.
9. Kok PW, Kwamanga DO. Cluster sampling for immunization coverage. *Soc Sci Med.* 1986;22: 781–783.
10. Ten Dam HG. *Surveillance of Tuberculosis by Means of Tuberculin Surveys.* Geneva, Switzerland: World Health Organization; 1985. Publication WHO/TB/85.145.
11. Arnadottir T, Rieder HL, Trebucq A, Waaler HT. Guidelines for conducting tuberculin skin test surveys in high prevalence countries. *Tuberc Lung Dis.* 1996;77(suppl):1–20.
12. Bennett S, Woods T, Liyanage WM, Smith DL. A simplified general method for cluster-sample surveys of health in developing countries. *World Health Stat Q.* 1991;44:98–105.
13. Cochran WG. *Sampling Techniques.* New York, NY: John Wiley & Sons Inc; 1977.
14. Roelsgaard E, Iversen E, Blocher C. Tuberculosis in tropical Africa. *Bull World Health Organ.* 1964;30:459–518.
15. Styblo K. *The First Round of the National Tuberculin Survey in Tanzania, 1983–1987. Tuberculosis Surveillance and Research Unit, Progress Report Volume 1, 1992.* The Hague, the Netherlands: Royal Netherlands Tuberculosis Association; 1992:127–164.
16. Rieder HL. Methodological issues in the estimation of the tuberculosis problem from tuberculin surveys. *Tuberc Lung Dis.* 1995;76: 114–121.
17. Styblo K. *Epidemiology of Tuberculosis. Selected Papers, Volume 24.* The Hague, the Netherlands: Royal Netherlands Tuberculosis Association; 1991.
18. Styblo K, Meijer J, Sutherland I. The transmission of tubercle bacilli. Its trend in a human population. *Bull Int Union Tuberc.* 1969;42: 5–104.
19. *Kenya Population Census 1989. Analytical Report Volume VIII. Population Dynamics of Kenya.* Nairobi, Kenya: Central Bureau of Statistics; 1996.
20. Elliott AM, Hayes RJ, Halwindii B, et al. The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. *AIDS.* 1993;7:981–987.
21. Nunn P, Mungai M, Nyamwaya J, et al. The effect of human immunodeficiency virus type-1 on the infectiousness of tuberculosis. *Tuberc Lung Dis.* 1994;75:25–32.
22. Cauthen GM, Dooley SW, Onorato IM, et al. Transmission of Mycobacterium tuberculosis from tuberculosis patients with HIV infection or AIDS. *Am J Epidemiol.* 1996;44: 69–77.
23. Murray CJ, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. *Bull Int Union Tuberc Lung Dis.* 1990;65:6–24.
24. Murray CJ, DeJonghe E, Chum HJ, Nyangulu DS, Salomao A, Styblo K. Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet.* 1991;338:1305–1308.
25. Fine PEM, Ponnighaus JM, Maine N. The distribution and implications of BCG scars in northern Malawi. *Bull World Health Organ.* 1989;67:35–42.