第 65 回 総会特別講演

IMPACT OF HIV INFECTION ON THE TUBERCULOSIS PROBLEM WORLDWIDE

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(Received for publication April 13, 1990)

INTRODUCTION

It is evident that persons infected with tubercle bacilli and with Human Immunodeficiency Virus (HIV) have an increased risk of tuberculosis (Pitchenik et al., 1984 ; Chaisson et al., 1987 ; Murray et al., 1987 ; Sunderam et al., 1986 ; Slutkin et al., 1988). Consequently, Worldwide tuberculosis elimination —which was near to becoming reality— will be seriously affected by HIV infection, particularly in Africa. The extent of the deterioration of the tuberculosis situation caused by HIV infection cannot yet be reliably estimated because the natural history of HIV infection is not well understood, neither in man nor in the community.

However, it is evident that in countries where both tuberculous and HIV infections are prevalent, an increase in new smear-positive, smear-negative and extra-pulmonary tuberculosis cases already exists, and the deterioration of the tuberculosis situation will continue for a number of years. The impact of HIV infection on the epidemiological situation of tuberculosis is so large that, under certain conditions, the tools available at present for tuberculosis control will fail to restrain the incidence of tuberculosis caused by HIV infection. The increased number of infectious tuberculosis cases due to HIV infection might result in an increase in the risk of tuberculous infection, with a further deterioration of the tuberculosis problem.

The impact of HIV infection on the epidemiological situation of tuberculosis will depend on several factors, in particular on :

1. the prevalence of HIV infection in the community and its trend ;
2. the prevalence of tuberculous infection in the general population aged 15–49 years ;
3. the breakdown rate from (remote) tuberculous infection to active tuberculosis ;
4. the level and the trend in the annual average risk of tuberculous infection ; and
5. the detection rate of new and relapse cases of tuberculosis and the cure rate of smear-positive cases.

1. PREVALENCE OF HIV INFECTION IN THE COMMUNITY AND ITS TREND

Reliable information on the level of and the trend in HIV infection among the general population in countries where HIV infection is prevalent is not readily available. The only information available worldwide are the data on AIDS, collected by the WHO Global Programme on AIDS. I shall present (i) the cumulative number of AIDS cases, (ii) the "incidence" of AIDS in 1987 and 1988, and (iii) the numbers and rates of AIDS for 6 African countries with the highest reported "incidence" rates during the period under study.

Although the number of cumulative AIDS cases

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Table 1. Cumulative AIDS cases reported to WHO from 1983 to 1988 as of 30.9.1989 and percent increase from one year to the next

Year	Africa N	Africa %**	Americas N	Americas %**	Europe N	Europe %**	Total* N	Total %**
1983	17		4,709		406		5,150	
1984	99		11,163		1,087		12,419	
1985	784	692	23,406	110	2,809	158	27,226	119
1986	4,104	423	43,536	86	6,308	125	54,471	100
1987	13,881	238	74,579	71	12,836	103	10,233	88
1988	32,651	135	111,259	49	22,070	72	167,676	64

* Total includes a further 376 cases reported in Asia and 1,329 cases reported in Oceania.
** Percent increase in cumulative AIDS cases reported compared with those reported in the previous year.

Table 2. AIDS cases and rates (per 100,000) reported to WHO for 1987 and 1988

Continent	1988 N	1988 Rate per 100,000*	1987 N	1987 Rate per 100,000*	Increase N	Increase %
Africa	18,665**	3.6	9,777	1.9	8,993	92
Americas	36,671	5.1	31,043	4.3	5,628	18
Asia	51	0.0	120	0.0	31	(26)
Europe	9,234	1.1	6,528	0.8	2,706	41
Oceania	514	1.9	397	1.5	106	27
Total	65,340	1.2	47,865	0.9	17,475	37

* Based on the 1988 population estimates (1988 World Health Statistics Annual p.77; WHO Geneva 1988).
** Incomplete data.

Table 3. Six countries with the highest rates on AIDS cases reported to WHO in WHO/AFRO regions in 1987 and/or 1988

Country	1987 N	1987 Rate per 100,000	1988 N	1988 Rate per 100,000
Congo	1,000	50.2	No report	
Uganda	1,789	9.7	4,072	22.1
Burundi	652	12.0	1,054	19.3
Malawi	860	10.2	1,582*	18.8
Zambia	345	4.1	1,057	12.5
Kenya	1,223	4.9	2,817	11.2

* Last report: 30.6.1988

reported to WHO up until 1988 has increased dramatically, the absolute number reported as of September 30, 1989 was "only" 167,676. Cumulative data for the period 1983 to 1988 are shown in Table 1.

It should be stressed that in spite of improved AIDS reporting in the last few years the doubling of the cumulative cases has slowed down ;

it took approximately 10 months to double the cumulative number of AIDS cases between 1984 and 1985, 12 months between 1985 and 1986, approximately 14 months between 1986 and 1987, and about 18 months to double the cumulative number of AIDS cases between 1987 and 1988 (the figures for 1988 in Table 1 are incomplete). This slowdown of the doubling time can be seen on all continents, even in Africa where case notifications are increasingly thorough.

Table 2 shows that the "incidence" of AIDS cases in Africa, both absolute numbers and rates per 100,000, are the second highest in the world. Estimated numbers for Africa for 1988 suggest that in 1990 or 1991 Africa will have the highest numbers and rates of AIDS cases in the world.

Table 3 suggests that in some African countries the rates of AIDS cases are very high and it can be expected that in a certain number of them the incidence (and death) rates will be higher than 100 per 100,000 in 1991.

There is considerable uncertainty in estimates of the current and future prevalence of HIV infection arising both from limited knowledge of key factors that determine transmission and disease progression, and from limitations in the epidemiological data. Salzburg and Dolina (1989) state that the ratio of the number of HIV carriers at the beginning of a given year to the number of cases of the acquired immunodeficiency syndrome (AIDS) diagnosed during the year is approximately 25. However, Brookmeyer and Goudert (1989) argue that this ratio does not remain constant throughout the epidemic and may vary among transmission groups.

HIV infection is currently unevenly distributed, with the highest prevalence in large cities or certain high risk groups, corresponding to Mann's pattern I and II (1988). The first pattern (I) affects certain groups, such as homosexual and bisexual men and intravenous drug users (Western Europe, North America, some areas in South America, Australia and New Zealand). Although heterosexual transmission does occur, it accounts for a much smaller portion of sexually acquired HIV infection than homosexual transmission. In pattern I areas transmission through blood principally involves intravenous drug users. Pattern II areas include large parts of Africa —mainly central, eastern and southern, but increasingly also western— and parts of the Caribbean. In these areas, sexual transmission is predominantly heterosexual and therefore the sex ratio for AIDS cases (and most probably also for HIV infection) is approximately equal. A very high risk group in pattern II are prostitutes (50–80% infected), and transfusion of HIV-infected blood is a public health problem, as is adequate sterilization of syringes and needles and other skin-piercing instruments. Finally, perinatal transmission is an increasing problem in these areas.

From the tuberculosis control programme point of view, pattern I of HIV infection is much less important than pattern II of HIV infection, since the former predominantly involves developed countries where prevalence of tuberculous infection in those aged 15–49 years is low.

Pattern II which is currently observed mostly in the major part of Africa will have considerable impact on tuberculosis and its control. Infants who represent in pattern II the second largest group of HIV-infected subjects will have no substantial impact on the epidemiological situation of tuberculosis and its trend, since an excess incidence of tuberculosis in small children primarily infected with tubercle bacilli will not increase transmission of infection and the vast majority of them will die, anyway, due to HIV. On the other hand, the remaining vast number of those with HIV infection are subjects aged 15–49 years, of whom a high proportion has been previously infected with virulent tubercle bacilli.

The latency period between HIV infection and the development of AIDS is variable. In more than 5,000 homosexual and bisexual males in San Francisco, the mean latency period was 7.8 years and it was estimated that 78 to 100% of HIV-infected men would develop AIDS within 15 years of infection (Hessol et al., 1988 ; Lui et al., 1988). A study of patients infected via blood transfusion has also demonstrated age-related differences in the mean latency period, with

children less than 5 years of age and adults 60 years and older having significantly shorter latency periods, 2 and 5.5 years respectively (Medley et al., 1987). It is possible that the latency period in Africans differs from that among San Francisco men.

2. PREVALENCE OF TUBERCULOUS INFECTION IN THE GENERAL POPULATION AGED 15 TO 49 YEARS

The prevalence of tuberculous infection in subjects aged 15–49 years depends on the level of the risk of tuberculous infection 50 years ago, and the average annual decrease in the risk of tuberculous infection during those 50 years up to the present day.

In developed countries the risk of tuberculous infection decreases by about 10 to 14% every year, i.e. it halved itself every 5 to 7 years during the last 40 years (Styblo, 1984). Consequently, the prevalence of tuberculous infection among those aged 20 to 50 years at present (1990) is relatively low (Styblo, 1989). For instance, in the Netherlands the prevalence of tuberculous infection in those aged 20 years is less than 0.4% and is approximately 12% at the age of 50 years (Figure 1). In 10 years from now, the figures will be under 0.1% and 4% respectively.

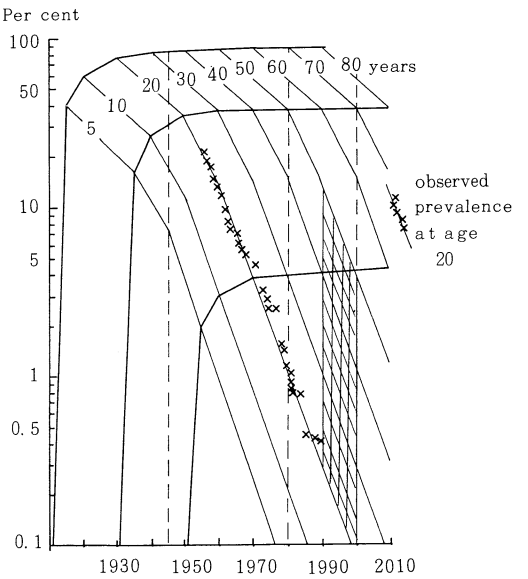


Fig. 1. Estimated percentage prevalence of tuberculous infection in cohorts born in 1930–1950

A simple way of estimating the prevalence of

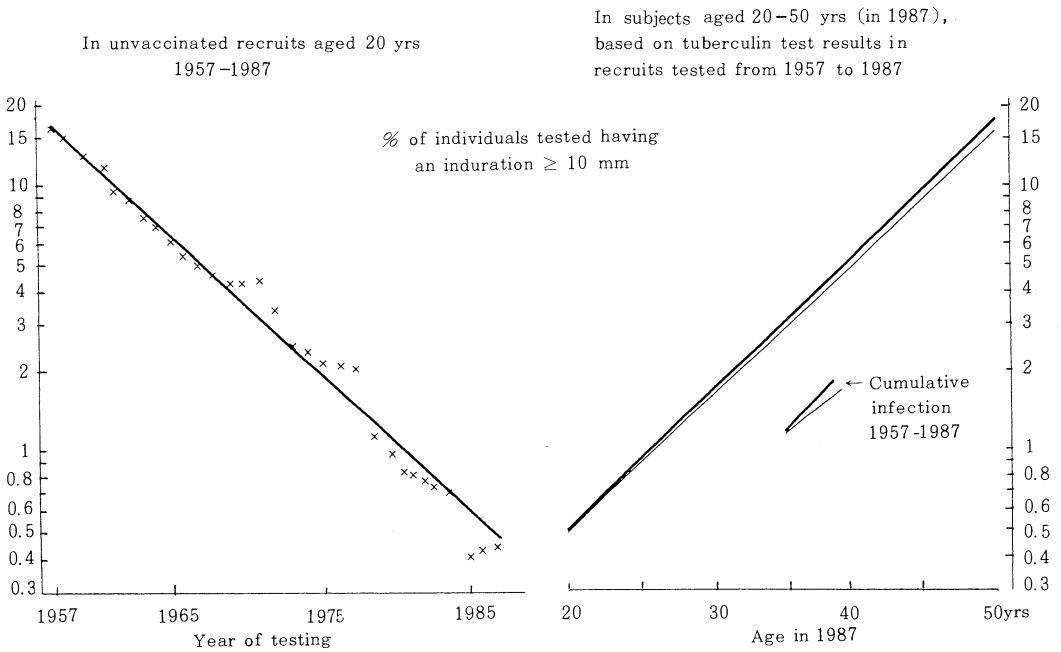


Fig. 2. Prevalence of tuberculous infection in the Netherlands

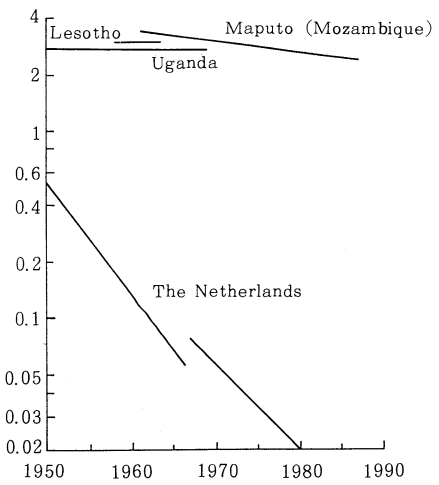


Fig. 3. Annual risk of tuberculous infection and their trend in high-prevalence countries, 1950–1987

tuberculous infection in subjects aged 20–50 years in the Netherlands can be derived from the prevalence of tuberculous infection in Dutch recruits aged, on average, 20 years. The data have been collected by Dr. Bleiker's Tuberculin Unit (TNO) in cooperation with the medical military authorities. Tuberculin surveys of recruits were introduced in the early 1950s and have been carried out by the same team on approximately 40,000 recruits annually, thus on more than 1,3 million subjects.

The left section of Figure 2 shows the prevalence of tuberculous infection in unvaccinated Dutch recruits aged 20 years for the period 1957–1987. The prevalence of infection was approximately 16.3% in 1957 and decreased to only 0.7% in 1984 and 0.5% in 1987. The corresponding annual risk of tuberculous infection was about 0.2% in 1957 and is very low at present (1989), less than 10 infections per 100,000 population per year. The right section of the Figure is a "mirror" of the prevalence of tuberculous infection observed in more than 1.3 million subjects over the period of 30 years. Those tested in 1957 at age 20 years were 50 years old in 1987 and were exposed to a decreasing risk of tuberculous infection, from 0.18% in 1958 to approximately 10 infections per 100,000 in 1987. The cumulative prevalence of infection acquired between 1957 and 1987 was lower than 2%, so that the 16.3% prevalence of infection found in 1957 in recruits aged 20 years increased to approximately 18% in 1987 when they reached their 50s. Those tested in 1985 were found to have a prevalence of infection of 0.6% and had virtually the same prevalence in 1987 at age 22 years.

It can be concluded that the two methods give very similar results of estimated prevalence of infection for the age-group up to 50 years.

Similar trends may be expected in Japan and other countries, most of which are about 10 to 15 years "behind" the Netherlands in terms of their tuberculosis situation.

The low prevalence of tuberculous infection in the population aged 15 to 50 years in developed countries suggests that HIV will have virtually no influence on the elimination of tuberculosis in low prevalence countries. Although a proportion of detected tuberculosis cases might have HIV infection or AIDS, their absolute number in young and middle-aged persons is very low, infectious tuberculosis in AIDS or HIV infected persons can be rendered non-infectious in nearly all cases, and contacts who have developed tuberculosis will be cured, with very few exceptions.

Unlike in developed countries, in most developing countries the annual decrease in the risk of tuberculous infection was very low during the last 4 decades, in some of them between 1 and 2 only : Uganda, Lesotho, Mozambique (Figure 3). A similar decrease has been observed in Tanzania. The first round of the National Tuberculin Survey was carried out between 1983 and 1987 and covered a representative sample of 80,000 children (Figure 4). Table 4 shows that the estimated risk of tuberculous infection in more than 34,000 non-BCG-vaccinated schoolchildren aged 10 years was between 1.1 and 1.2%. Compared with the risk for the same age in 1957 the present risk of infection (1985) suggests that there was an annual decrease in the risk of infection between 1 and 2% during the period under study. It is evident that the prevalence of tuberculous infection in subjects aged 20 to 50

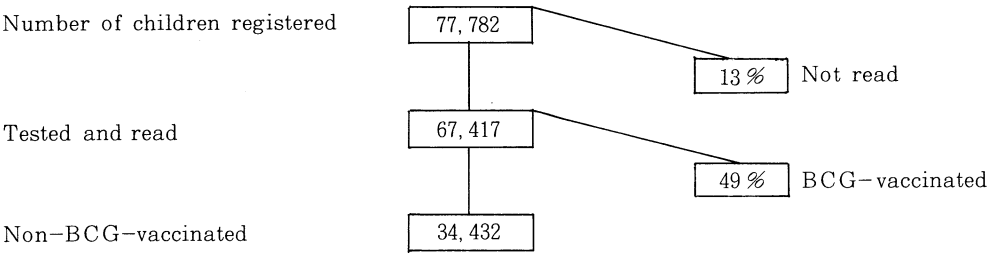
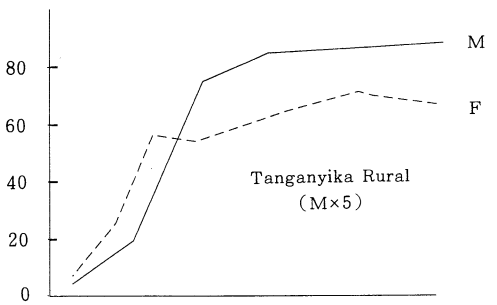


Fig. 4. The number of schoolchildren registered, tested and read, and the proportion of BCG-vaccinated children (the average age of non-BCG-vaccinated children was 9.8 years) in the NTS, 1983—1987.

Table 4. The estimated risk of tuberculous infection in 34,432 non-BCG-vaccinated schoolchildren (aged 10.3 years) based on the observed and the 'Weighted' prevalence by estimated populations per region, assuming a 1% and 3% decrease in the risk of tuberculous infection.

	Prevalence of tuberculous infection:					
	Observed in the survey			'Weighted' population per region		
	Induration (mm)			Induration (mm)		
	≥10mm	≥14/0.82mm	≥17×2 mm	≥10 mm	≥14/0.82mm	≥17×2 mm
Prevalence at 9.6 years	13.5%	10.4%	11.1%	14.2%	10.9%	11.6%
Risk of infection:						
at a 1% decrease	1.3%	1.0%	1.1%	1.4%	1.1%	1.1%
at a 3% decrease	1.2%	0.9%	1.0%	1.2%	0.9%	1.0%



From Roelsgaard et al., Bull. Wld. Hlth. Org. 1964, 30:459-518

Fig. 5. Estimated prealence of tuberculous infection in Tanganyika, 1957

years at present is similar to that observed in WHO tuberculosis survey in the late 1950s (Figure 5).

Thus we can conclude that in the major part of Africa more than 50% of persons aged 15 to 50 years have been infected with tubercle bacilli. Moreover, a relatively high proportion of young persons who have not yet been infected with tubercle bacilli are exposed to a substantial risk of primary infection. It is thus inevitable that the absolute number of cases of tuberculosis in developing countries will increase in those countries where AIDS is a major problem.

3. BREAKDOWN RATE FROM TUBERCULOUS INFECTION TO ACTIVE TUBERCULOSIS

Although the great majority of the patients with tuberculosis and HIV infection or AIDS arise from endogenous reactivation of the remote tuberculous infection, a proportion of those primarily infected among HIV-positive subjects also develop active tuberculosis.

The first essential step in assessing the size of tuberculosis problem in HIV-positive patients is therefore to know in what proportion of subjects, infected in the past with tubercle bacilli, the bacilli survive in a form capable of reactivation following HIV infection. It is estimated that at least 30% of past tuberculous infections will be reactivated following HIV infection (Sutherland, 1989).

An increasing incidence of tuberculosis has been observed in several IUATLD-assisted National Tuberculosis Programmes in Africa in the last few years.

Table 5 shows the number of reported cases in Tanzania from 1979 to 1988. The table suggests that an average of 7,800 smear-positive new cases and 550 relapses were diagnosed annually, in addition to 3,550 smear-negative and 1,500 extra-pulmonary cases with a mean total of 13,400 cases diagnosed per year. However, the figures were substantially higher for 1988.

Figure 6 shows the numbers of cases reported to the Ministry of Health in Malawi from 1985 to 1988. While the total number of cases reported in 1985 was slightly over 5,000, the number in 1988 exceeded 8,000 cases, an increase of 59% in 3 years. The number of smear-positive cases increased by 43% in the same period. It should be stressed that the sharp increase was caused not only by HIV infection but also by an influx of refugees from Mozambique and the favourable influence of good results of short-course chemotherapy.

It remains to be seen to what extent the larger number of tuberculosis cases among AIDS patients or HIV-infected persons will worsen the transmission of tuberculous infection. This problem will be studied in Tanzania and Malawi.

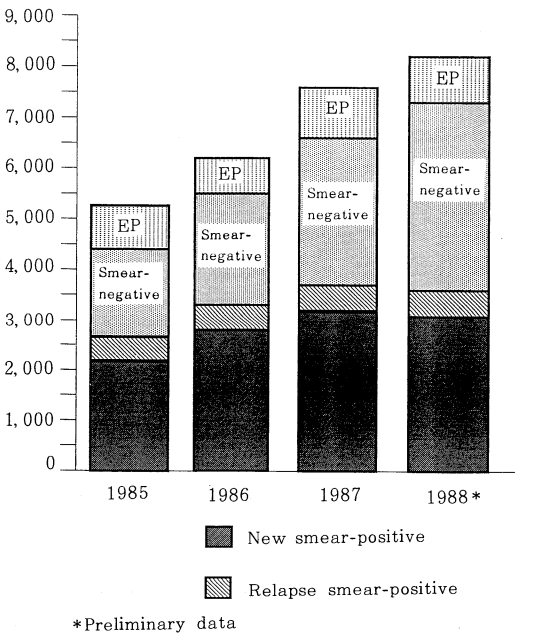


Fig. 6. Tuberculosis cases (all forms) reported in Malawi from 1985 to 1988

4. THE LEVEL OF THE ANNUAL AVERAGE RISK OF TUBERCULOUS INFECTION AND ITS TREND

Although a sharp increase in tuberculosis inci-

Table 5. Total numbers of reported cases in Tanzania over 10 years (1979—1988)

	Reported cases	
	1979—1988	Of them in 1988*
Smear-positive : new	7,800	9,800
relapses	550	700
Subtotal	8,350	10,500
Smear-negative	3,550	4,700
Extra-pulmonary	1,500	2,800
Total	13,400	18,000

* Preliminary figures.

dence has been observed in several developing countries where both tuberculous and HIV infections are prevalent, it is very probable that the transmission of tuberculous infection will not increase accordingly. As already mentioned, the increased tuberculosis incidence is mainly due to the depression of cellular immunity caused by HIV infection in subjects previously infected with tubercle bacilli, and only to an extent due to recent infections in previously uninfected subjects or reinfections in those previously infected.

However, if the current risk of tuberculous infection is high and the annual decrease in the risk is low, the excess infectious tuberculosis cases caused by HIV will gradually increase the risk of tuberculous infection (Figure 3).

In conclusion, the current level of the risk of tuberculous infection and its trend is the most decisive factor in containing the deterioration of the epidemiological situation of tuberculosis caused by HIV in the future.

5. HOW TO CURB THE INCREASE IN TUBERCULOSIS CASES CAUSED BY HIV INFECTION ?

The only way to curb the increase in tuberculosis cases caused by HIV infection is :

(i) to scrupulously maintain the high detection rate and a high cure rate of smear-positive cases achieved in IUATLD-assisted National Tuberculosis Programmes in poor developing countries in Africa, and

(ii) to cope with the substantial increase of tuberculosis cases caused by HIV infection until the epidemic of HIV infection in a respective population will eventually stabilize at a certain level or start to decrease.

Considerable improvement of the cure rate of smear-positive cases (both new and relapses) is undoubtedly one of the most, if not the most important success in the IUATLD-assisted National Tuberculosis Programmes. This has been possible through the introduction and gradual mass application of relatively inexpensive short-course regimens for :

- new cases 2SHRZ/6TH
- relapses 2SHRZE/1HRZE/5H3R3E3

Table 6 shows the results achieved in Tanzania in patients enrolled on short-course chemotherapy from April 1982 to June 1988. The left-hand part of the table refers to the results presented in Singapore in 1986 when 5,781 cases were evaluated. The right-hand part of the table shows the results in 24,121 cases (the data reported in Singapore are included in the latter figures). The success rate of 77% is nearly 25% better than that achieved by standard chemotherapy during the first 4 years of the programme.

If the 7% of patients who died are removed from the denominator the bacteriologically documented cure rate is 82% (Table 7). If sputum conversion likely to have occurred in a proportion of those from "transferred out" and "absconded" is taken into consideration, the cure

Table 6. Results of short-course chemotherapy at 8 months in 24,121 new smear-positive cases (Tanzania)

	April 1982 to 1985 Reported in Singapore, 1986	April 1982 to June 1988
No. enrolled	5,781	25,469
of them "false positive"	231 (4 %)	1,348 (5 %)
Evaluated	5,550 (100 %)	24,121
	Results (in %)	
Negative	75.5	77
Positive	3.5	2
Died	6	7
Absconded	12	10
Transferred out	3	4

Table 7. Results of short-course chemotherapy in 22,546 new smear-positive patients who were alive 8 months after the start of chemotherapy Tanzania, April 1982 – June 1988.

	%
Negative	82
Positive	3
Absconded	11
Transferred out	4

If sputum conversion likely to have occurred in a proportion of those from "transferred out" and absconded is taken into consideration, the cure rate might be close to

90 %

rate might be close to 90%.

From the available data as of now it has become evident that tuberculosis patients increasingly represent a group that identifies with a high probability with HIV infection and vice versa. Case finding activities for both infectious and non-infectious tuberculosis will have to be intensified to contain transmission, to cure patients and prevent unnecessary deaths where feasible, a formidable task that lies ahead with the HIV epidemic in sub-Saharan Africa.

In Asia, HIV infection is still relatively low. It is important whether HIV infection in Asia will spread in the general population and to what extent, since the epidemiological situation of tuberculosis worldwide will depend on the increase in tuberculosis cases caused by HIV infection in Asia where most tuberculosis cases develop at present. It is, therefore, essential to achieve in all Asian countries a distinct decrease in the risk of tuberculous infection, the most decisive factor in containing possible adverse effect of HIV in the future.

Tokyo, March 1990

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