Tuberculosis control in Hong Kong

Historic perspective

Tuberculosis (TB) is an old disease. Fragments of the spinal column from Egyptian mummies show evidence of TB over four thousand years ago. Large-scale epidemic of the disease occurred in the recent centuries. In 1958, Grigg pointed out that the shape of the epidemic curve for TB is the same as that for any other infectious disease, if one adjusts the time scale to allow for the roughly 300-year duration of a TB epidemic.[1] The TB epidemic started in Europe over three centuries ago. The TB morbidity and mortality began to fall well before introduction of BCG vaccine and effective treatment. The TB epidemic in Asia started much later, and hence is probably in a different epidemiological stage as compared to the rest of the developed world.

The introduction of sanatorium care in the mid-nineteen century provided the first real step in the battle against this dreadful disease. In 1882, Robert Koch discovered the tubercle bacillus, but few weapons were available against this important human enemy. Artificial pneumothorax and other surgical methods to reduce the lung volume were developed in the late 19th century. Subsequently, the French bacteriologist Calmette, together with Guerin, used specific culture media to lower the virulence of the bovine TB bacterium, and there came the BCG vaccine still in widespread use today. In 1943, streptomycin was discovered and in the next year, it was administered for the first time to a critically ill TB patient with very impressive effect. However, with streptomycin monotherapy, resistant mutants began to appear within a few months. Other anti-TB drugs were subsequently introduced, and it was soon demonstrated that emergence of resistant mutants could be prevented with a combination of anti-TB drugs.

In Hong Kong, TB became a notifiable disease in 1939. In 1947, the first public service for TB was established at the Harcourt Health Center followed by a few subsidiary clinics in Aberdeen, Stanley, Tai Po and Yuen Long. The Kowloon Chest Clinic was opened in 1951, and the Wanchai Chest Clinic replaced the Harcourt Health Centre in 1954. Initially, these centers provided limited facililties, such as provision of vitamins, tinned food, milk powder and rice. A restricted number of artificial pneumothorax and artificial pneumoperitoneum were done. In 1951, major surgery for TB was started, and later thoracoplasty and lung resection were conducted.

Specific treatment with anti-TB drugs was first introduced in 1950, with the use of PAS (para-aminosalicylic acid). Later streptomycin was introduced in 1951 and isoniazid in 1952. Effective combination chemotherapy then became available. However, in the 1950's and 1960's, only about one quarter of the patients completed treatment and the danger of unsupervised treatment became increasingly recognized. Supervised treatment, which was the forerunner of directly observed treatment (DOT), was introduced on a trial basis in 1960's. Since 1970's, the supervised treatment was delivered as part of the TB service. The 6-month standard four-drug short course regimen with isoniazid, rifampicin, pyrazinamide, and streptomycin (or ethambutol) was introduced as early as 1979.

The recent tuberculosis situation

The World Health Organization (WHO) has estimated that eight million people get TB every year, of whom 95% live in developing countries. An estimated two to three million people die from TB every year.

In industrialized countries, the steady drop in TB incidence began to level off in the mid-1980s and then stagnated or even began to increase. Much of this rise can be at least partially attributed to a high rate of immigration from countries with a high incidence of TB. Forty-one percent of the notifications in England and Wales in 1993 were in those of Indian subcontinent origin. Their notification rate was 128 per 100,000 in 1993, nearly 30 times that of the white population. The highest rates were in those entering the United Kingdom, within previous 5 years, followed by those entering 6 to 10 years before, but rates were higher than those rates in the white population at all ages, including those born in the United Kingdom.[2] In the United States, routine surveillance indicated that from 1986 to 1995, foreign born cases of tuberculosis in the United States increased by 61%, and foreign-born cases as a percentage of all cases increased from 22% to 35%.[3]

While only one out of ten immunocompetent people infected with Mycobacterium tuberculosis will develop active TB in their lifetimes, among those infected with HIV, one in ten per year will develop the disease. In many industrialized countries, this is certainly a tragedy for the patients involved, but these cases make up only a small minority of the TB cases. However, in developing countries, the impact of HIV infection, especially in the 20 - 35 age group, is of increasing concern. The combined attack by these two dreadful pathogens can be devastating on the health of the population as well as the vitality of the economy.

Drug resistance in TB occurs as a result of tubercle bacillus mutations. Since it is very unlikely that a single bacillus will spontaneously mutate to become resistant to more than one drug, giving multiple effective drugs simultaneously will inhibit the multiplication of these resistant mutants. Unfortunately, patients may be denied of or fail to complete an effective combination regimen in many parts of the world. Therefore, the emergence of multi-drug resistance is an area of growing concern.

The notification rate of TB in Hong Kong has shown an overall downward trend in the past 40 to 50 years (Figure 1). The rate decreased from a peak of 697.2 per 100,000 in 1952 to around 100.9 in 1995, and thereafter ran a fluctuating course. With the rapid decline in disease incidence brought about by effective treatment in the last few decades in Hong Kong, there has probably been decreasing exposure to the tubercle bacilli for successive birth cohorts. The notification rate for young children under 5 years old tends to reflect the on-going risk of infection. Although the absolute numbers may have been affected by the almost universal neonatal BCG vaccination undertaken locally, it is reassuring to note the drastic decline from 38.8 per 100,000 in 1965 to only 6.4 per 100,000 in 2000 (Figure 2). The decreasing tuberculin-positive rate among the 6- to 9-year olds from 79.5% in 1967 to 16.9% in 2000 also strongly suggested a very significant decline in the risk of infection (Figure 3).

The population of Hong Kong is getting older as it undergoes demographic transition, which is a result of decreasing birth rate and increasing life expectancy. 3.6% of the population was aged 65 or over in 1965, and the corresponding figure in 2000 was 10.9% already. With the high prevalence of TB in Hong Kong and Mainland China in the past decades, many of our elderly are likely to have been exposed to the tubercle bacilli in the past. With an aging population and the relative affluence of the society, chronic degenerative diseases are increasingly encountered. In a survey conducted by the TB & Chest Service in August 1999, about 25% of all notified TB cases were found to have medical conditions that could predispose to the development of TB. These included diabetes mellitus, malignancies, chronic renal failure, treatment with cytotoxics and steroids, silicosis, and others. While there was a declining trend in the overall TB notification rate in the past five decades, the actual number of notifications for those aged 65 or above increased from 1158 (15.3% of total notifications) in 1985 to 2867 (37.8% of total notifications) in 2000 (Figure 4). The factors that underscore such significant change in the profile of patients may also help to explain why Hong Kong is experiencing stagnation of the TB trend in the recent decade, just like other places with intermediate TB burden, e.g., Japan, Singapore, and Malaysia (Figure 5).

The recent fluctuation in TB notification trend has raised some concern about TB resurgence locally. From the rate of 100.9 per 100,000 in 1995, the notification rate increased in three consecutive years to 101.0 in 1996, 109.0 in 1997, and 117.3 in 1998. In terms of actual numbers, there were 7,673 notified TB cases in 1998 as compared to 6,212 cases in 1995, representing an increase of 1,461 cases or 23.5%. In the same period, the population increased only by 6.3%. However, there were also significant changes in the distribution of notification sources (Figure 6). While the number of notifications from chest clinics and chest hospitals remained more or less the same, being 5,659 in 1995 and 5,824 in 1998, notifications from general hospitals and the private sector more than tripled from 553 to 1,842 in the same period. Such drastic increase probably reflected a positive change of notification behaviour among these previously minor notification sources and the additional 1,289 cases could almost account for all the increase in notifications from 1995 to 1998. In 1999, the number of notified cases fell again to 7,512, resulting in a notification rate of 113.7 per 100,000. The provisional figures for 2000 were 7,578 and 113.7 per 100,000 respectively.

Only 152 cases in 2000 involved recent immigrants from Mainland China (Figure 7). These recent immigrants did not appear to be at excess risk of TB in comparison with the local population. Only 7 cases involved Vietnamese boat people in contrast to higher numbers in the previous years, probably reflecting the decreasing size of this segment of the population (Figure 8). Overall, these immigrant groups only represented a very small proportion of the total caseload. This is in sharp contrast to the situation in many western countries. The much smaller differences in disease risk between the indigenous population and the immigrant groups in Hong Kong may largely account for such observation.

At present, HIV-related TB cases represent only a small minority of the annual TB notification. Unlinked anonymous testing has shown that only 0.5% of the TB patients in the chest clinics were HIV seropositive (Figure 9). There has been a slow rising trend over the years, probably because increasing number of HIV-infected persons have developed AIDS with the passage of time as the HIV epidemic matures.

TB mortality declined from a peak of 207.9 per 100,000 in 1951 to 4.5 per 100,000 in 2000 and TB is now outside the top ten causes of death (Figure 10). The average age at death increased from 25 years in 1951 to 74 years in 2000. While part of the dramatic decline of TB mortality may be attributed to decreasing incidence of the

disease, effective management of TB patients must have been another major contributing factor. Effective chemotherapy in the form of DOT cured many ill patients, and averted many deaths. Increased awareness by both patients and health care workers could have led to earlier diagnosis, and allowed treatment at an earlier stage. However, delay in seeking care, atypical presentation, poorer drug tolerance, co-existing diseases, and psychosocial problems were likely factors that had contributed to the less favourable outcome among the elderly.

Present tuberculosis services in Hong Kong

In Hong Kong, public services for TB patients can be broadly classified into primary and secondary levels. The Department of Health (DH) is responsible for the primary level care with the services delivered through its 18 chest clinics (12 full time and 6 part time). The great majority of TB patients in Hong Kong are being managed here for ambulatory outpatient care. As regards secondary level care, which is basically the inpatient hospital management, the Hospital Authority takes the major role mainly through its 5 chest hospitals, namely Grantham Hospital, Ruttonjee Hospital, Kowloon Hospital, Wong Tai Sin Hospital and Haven of Hope Hospital. The interrelationship of the various services is illustrated in Figure 11.

Apart from clinical services, TB laboratories are also an essential component. The Yung Fung Shee TB Laboratory (YFSTBLab) handles about 80 to 90% of the specimens from TB patients in Hong Kong. The other laboratories with special tests like sensitivity testing for TB are the Grantham Hospital, Ruttonjee Hospital, and Haven of Hope Hospital.

The Tuberculosis & Chest Service (TB&CS) of DH plays a key role in the public health control of TB in Hong Kong. Apart from primary level clinical services, its domain of activities covers the surveillance of TB, case finding, supervised chemotherapy, defaulter tracing, contact tracing, BCG vaccination, health education and research.

Tuberculosis control strategies

Broadly speaking, the core components of TB control strategy include case finding, effective chemotherapy, treatment of latent TB infection, BCG vaccination, and health education.

Case finding

Mass Screening

In a series of studies conducted between 1960 and 1973, it was shown that even in places with active case-finding programmes, about 60% of sputum smear-positive patients were discovered because of their symptoms.[4,5] Only 20% of new cases were found through indiscriminate mass radiography alone.[4] This is explained by the relative rapidity with which infectious cases develop, faster than repeat screening can be accomplished. Mass chest x-ray screening has been abandoned in many places including Hong Kong in the mid-1970's upon WHO's recommendations because of its low cost-effectiveness.[6] A more recent evaluation of the national TB programme in India also concluded that x-ray and smear microscopy should not be used indiscriminately as case-finding tools in mass case-finding programmes, because their predictive values of positivity are likely to be very low at the prevalence rates of 200 to 800 per 100,000 in that community.[7]

Active screening among high-risk groups

While mass screening of asymptomatic individuals is no longer advocated, active screening of selected high-risk groups are practised in low-incidence countries. Two major groups may be targetted for screening activities, firstly persons with a high risk of TB in need of curative treatment; and secondly, persons at high risk of developing TB later who may benefit from preventive intervention.[8] Target groups may include immigrants and refugees from high-incidence countries,[9,10] inner-city marginalized populations,[11] inmates of correctional facilities[12] and other groups as determined by local epidemiology. Given the incomplete knowledge on high TB risk groups, and limitation of existing diagnostic tools, active case finding may not be cost-effective in most countries.[13]

Currently in Hong Kong, active screening is being carried out mainly for the group of close contacts of TB patients. Even among the household contacts, a commonly recognized high-risk group, the yield of active TB is only in the order of 1% (Figure 12). The yield of infectious bacteriologically positive cases is much lower at 0.14%. It is therefore prudent to exercise due caution in introducing any large-scale active case-finding programme, as resources so invested may have much better alternative uses.

Although screening of immigrants is commonly practised in low-incidence country, there is probably little role for such screening in Hong Kong as a result of the following two observations:

1. very low proportion of cases are attributable to recent immigrants (Figure 7);
2. absence of increased risk for recent Chinese immigrants.

As for screening of other groups such as elderly in institutions, and prison inmates, the diagnostic tool to be employed, the role of treatment of latent infection, and the question of cost-effectiveness must be carefully addressed before such screening can be applied on a service basis.

Passive case-finding

Passive case-finding, i.e., picking up the disease in those symptomatic patients coming forward for treatment (symptom motivation), has been shown to be more cost-effective in most control programmes and accounts for over 90% of the detected TB cases. It has been shown in a number of studies that smear-positive patients were the main infectious sources and over 90% of these patients have symptoms, predominantly cough.[4,5] It has also been shown that examination of symptomatic patients give a much higher yield than screening of asymptomatic individuals[7]. The WHO TB control strategy therefore stresses on case detection through passive case finding, i.e. detection of TB cases among persons presenting themselves to a health worker with symptoms indicative of TB[6]. In high-incidence countries, especially where resources are limited in comparison with the size of TB problem, passive case-finding must remain the primary strategy in detecting infectious new TB cases. Passive case-finding has been the mainstay of the local case-finding activities. A walk-in approach has been employed by the chest clinics. Free diagnostic and treatment services are offered at multiple convenient sites by the 18 chest clinics.

Effective chemotherapy

The most effective preventive measure for the control of TB is to stop it at the source. The source of TB spread is sick and infectious TB patients. Effective treatment of infectious TB patients is therefore the most important component for TB control. Non-compliance with treatment is the commonest cause of treatment failure, and is common with the long course of treatment necessary for TB. Therefore, the use of directly observed treatment, short course (DOTS) is strongly recommended by

WHO in the control of TB. DOTS has five key components:

1. government commitment to sustaining TB control;
2. case detection by sputum smear microscopy among symptomatic patients;
3. a standardised treatment regimen of six to eight months for at least all confirmed sputum smear-positive cases, with directly observed treatment (DOT) for at least the initial two months;
4. a regular uninterrupted supply of all essential antituberculosis drugs; and
5. a standardised recording and reporting system that allows assessment of treatment results for each patient and of the overall TB control programme.

Hong Kong was among the first to pioneer with DOT in the 1960/1970's, largely in response to low treatment completion rate and mounting resistance at that time. The short course treatment regimen was introduced in 1979. A highly efficacious regimen comprising six months of treatment was used. This consisted of four drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol) in the initial phase, followed by two drugs (isoniazid and rifampicin) in the subsequent continuation phase. As a result of these measures, the majority of TB patients managed to complete the full course of treatment. Resistance to anti-TB drugs started to fall (Figure 13). The success of these early trials, undertaken with the British Medical Research Council in Hong Kong and other places, laid the foundation of the current WHO recommendation. The cost for providing DOTS is justifiable in view of a higher cost being saved by avoiding the need to manage many patients with destroyed lungs, treatment failures, disease relapses and the spreading epidemic of multi-drug resistant TB that have been witnessed in certain communities.

DOTS may not work on its own as exemplified by two recent studies under in South Africa and Parkistan.[14,15] Community acceptance, a committed team of staff and measures to promote adherence by convenient location, convenient hours, education, counselling, rapid defaulter identification, exhaustive defaulter tracing, and even incentives are all essential to allow the system to work. Even with our existing arrangement, there remain a significant percentage of treatment defaulters at a rate of around 4% for new treatment cases and 8.5% for retreatment cases. As defaulters pose a potential persistent source of infection in the community, continuing effort is called for to further reduce this in the years to come.

Treatment of latent tuberculosis infection

It is estimated that 2 billion people worldwide have latent TB infection (LTBI).[16]

Most cases of active TB arise in people with LTBI. Although the risk is highest in the first two years after infection, the risk persists for their lifetime. In contrast with the DOTS strategy, improved diagnosis and treatment of LTBI has the potential to tackle the large pool of infected individuals across successive birth cohorts, and thereby to bring the disease under more rapid control.

Traditional treatment of LTBI has typically involved the use of isoniazid for 6 to 12 months. With the reported efficacy of a 2-month course of rifampicin plus pyrazinamide in the treatment of LTBI among the HIV-infected individuals, there has been revived enthusiasm in adopting such an approach. The American Thoracic Society (ATS) and the United States Centres for Disease Control and Prevention (CDC) issued a joint statement in 2000 entitled "Targeted tuberculin testing and treatment of latent tuberculosis infection" to guide clinicians in the care of people with LTBI.[17] Emphasis was duly put on directing tuberculin testing to populations at risk instead of offering broad screening, more treatment options, including short-course rifampicin-based regimens, and simplified monitoring of treatment that emphasises clinical evaluation more than laboratory examination. While there has been some preliminary evidence that patients receiving the short-course rifampicin plus pyrazinamide regimen were more likely than patients receiving long-term isoniazid to start treatment and to complete treatment,[18] side-effects, especially hepatitis, remain an important concern. Indeed, case reports of fatality from drug-induced hepatitis associated with the short-course rifampicin plus pyrazinamide regimen has prompted revision of the guidelines in August 2001 to ensure closer monitoring and better patient safety.[19]

Imperfect diagnostic tool, long duration of treatment and potential serious side-effects are inherent difficulties in the current approach to treatment of LTBI. Problem of motivation in symptomless people, adverse social factors among risk groups, and the huge infected pool render it almost impossible to apply such an approach on a wide service scale in most high-incidence areas. However, even in these areas, identifying those at increased risk of progression to active disease, improved screening, diagnosis, and treatment of LTBI are still called for, especially for selected high risk groups like those with HIV infection or other immune-compromising conditions.

Treatment of LTBI has not been very widely practised in Hong Kong, partly because of the difficulty in interpreting a positive tuberculin response within a community with very wide BCG coverage, and partly because of the potential problems of drug compliance and drug reaction with prolonged course of treatment. However, in the

Government TB&CS, treatment of LTBI or chemoprophylaxis is regularly offered to all infant close contacts of smear-positive patients, and also to similar contacts aged from 1 to 4 (under 5) if the tuberculin response is 15 mm or greater, or if there is documented tuberculin conversion (Figure 14). Treatment of LTBI is also offered to tuberculin-positive HIV-infected individuals and tuberculin-positive silicotic patients. The role of treatment of LTBI is currently being assessed in older children contacts.

BCG vaccination

The practice of BCG vaccination varies widely in different parts of the world. Some countries do not give BCG vaccination regularly, while others vaccinate all infants at birth. The efficacy of BCG vaccination in newborns is well recognized and the topic has been reviewed by Colditz et al recently.[20] It is particularly useful in the protection against disseminated TB such as TB meningitis and miliary TB.[21,22] However, the efficacy of BCG revaccination in older individuals is in doubt.[23-30]

In Hong Kong, BCG vaccination was first introduced in April 1952 as an organized campaign by the government with technical and material assistance from the UNICEF (United Nations International Children's Emergency Fund) and the WHO. Over the years, the BCG vaccination programmes have been modified according to the local situation, availability of up-to-date scientific information, and international recommendations. For the past few decades, the BCG team of the TB&CS has been offering the vaccination to two main target groups: the newborns and the primary school students.

The coverage for newborn babies has been persistently over 98% since 1980 (Figure15) and this has contributed significantly to the low rate of TB among the young age group locally (Figure 2). On the other hand, a statement was issued by WHO in 1995 stating that there is no proven value for BCG revaccination and it is not recommended. Hence, a review of the local BCG revaccination programme for primary school children has been carried out. As the data did not suggest any additional protective efficacy offered by the revaccination,[31] the programme has been stopped recently in the school year starting from September 2000.

Hence, the current policy is to vaccinate the newborn babies, as well as children residing in Hong Kong and aged under 15 without any prior BCG vaccination. Repeated doses of BCG vaccination are in general not recommended in any individuals.

Health education

Although some groups may be at greater risk of developing TB, no one is completely free from risk. This clearly applies to Hong Kong where TB is prevalent. Therefore, a population approach has to be adopted in health education, in addition to activities focusing on potential risk groups.

Health education of the public is crucial to promote passive case finding. Messages relayed to the public include the nature of the disease, the symptoms suspicious of TB, the available local services for TB, the treatment, the preventive and the rehabilitative measures. Clearing of common misunderstandings also helps to reduce the stigma and consequential discrimination, which is a critical barrier to access of care.

Announcements of public interest in TV and radio have been launched to encourage those with chronic cough and other symptoms suggestive of TB to come forward for examination. In collaboration with the media and professional associations, educational programmes on TB also appear from time to time on TV and radio. The World TB Day on March 24th each year offers good opportunity for TB exhibition, health talk and other awareness-promoting activities. In addition, health talks are organised from time to time in schools, elderly homes, homes for the handicapped, and other institutions. Posters, pamphlets and leaflets are other tools frequently employed for public health education. CD-ROMs on control of infectious diseases (including TB) for schools have been developed by DH. In addition, development of CD-ROMs targeting at the general public has been carried out in collaboration by the Hong Kong Tuberculosis, Chest and Heart Diseases Association and TB&CS.

Promoting awareness of TB is equally important among health care workers. In a study undertaken by Medical Research Council in Kenya, 90% of TB suspects attended a health care facility for an average of more than 5 times, yet 65% had neither chest x-ray or sputum examination done.[32] TB shares symptoms with many common respiratory conditions. Unless the attending doctor or health worker is alert of the possibility of TB, and order appropriate investigations, TB patients coming forward with symptoms will remain unidentified. Continuing medical education is also essential to ensure that the essential public health functions like notification, contact screening, and DOT are clearly understood, and TB patients are given timely and effective treatment. Therefore, TB articles are published in professional journals and the Epidemiology Bulletin of the Department of Health from time to time. In

collaboration with other organizations, seminars on TB are also provided for doctors and other health care workers. A TB website is under development which will target health care professionals in addition to the public. A CD-ROM on TB will also be prepared and sent to all doctors in Hong Kong.

Summary

Case finding, effective chemotherapy, treatment of LTBI, BCG vaccination and health education are the core components of the local TB control strategy. Implementation of these control measures has brought about major reduction in the TB morbidity and mortality statistics in the past decades. However, with the changing demography, increasing prevalence of chronic degenerative disease, high population density, and rapid population movement, there are new challenges to meet. Continuous evaluation and refinement of the existing measures is called for. Greater investment in research and development is also desirable in order to bring along new initiatives in the frontiers of our long battle with the tubercle bacillus.

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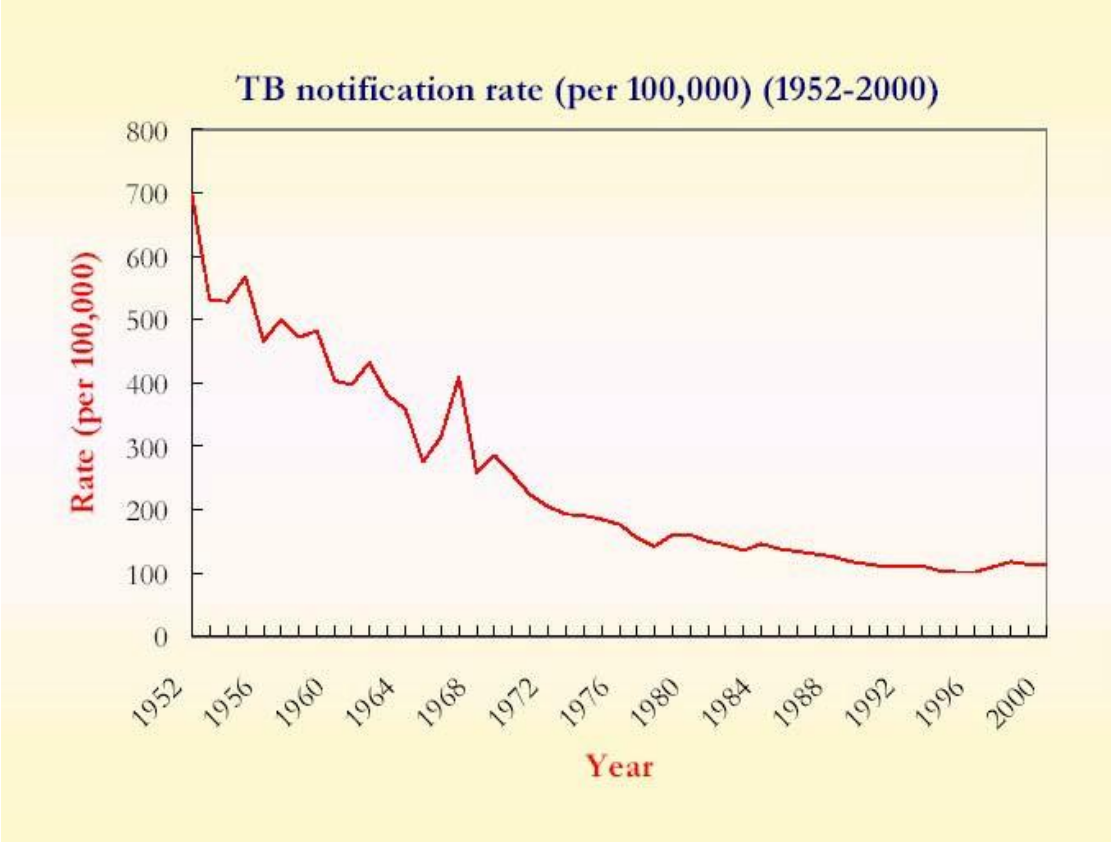

Figure 1. Notification rate of TB in Hong Kong

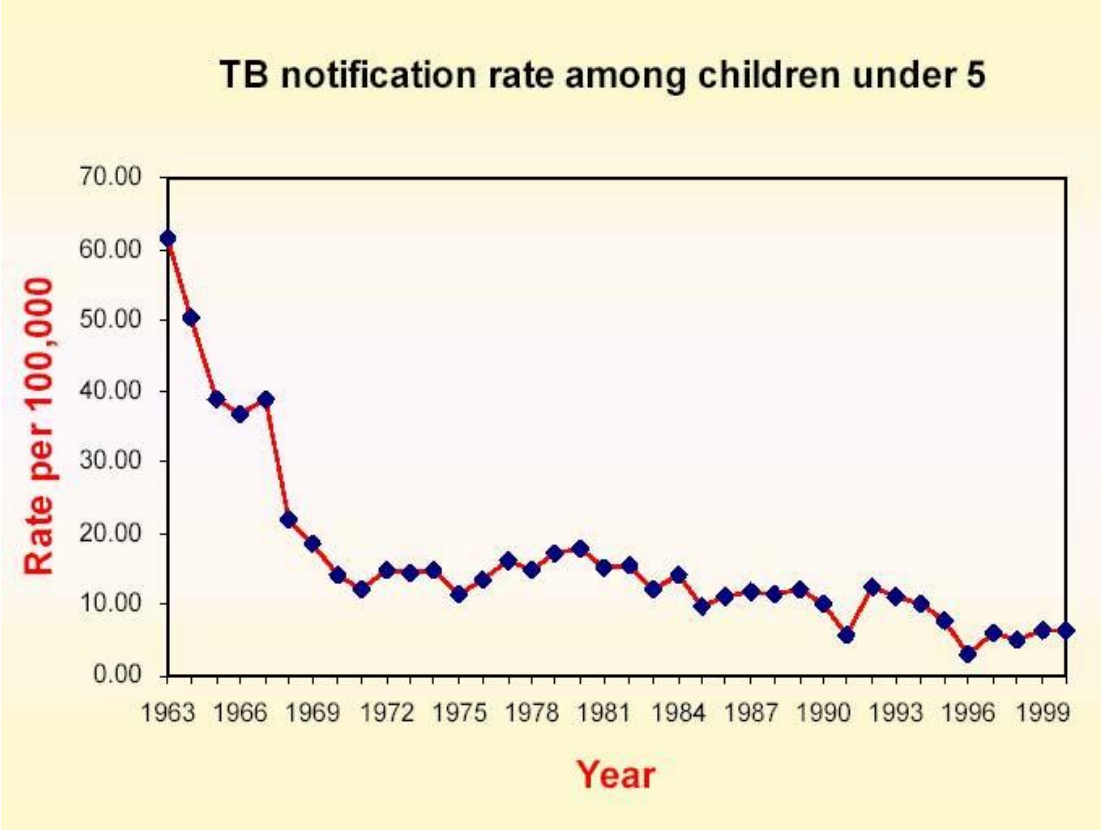

Figure 2. TB notification rate for young children under 5 years old in Hong Kong

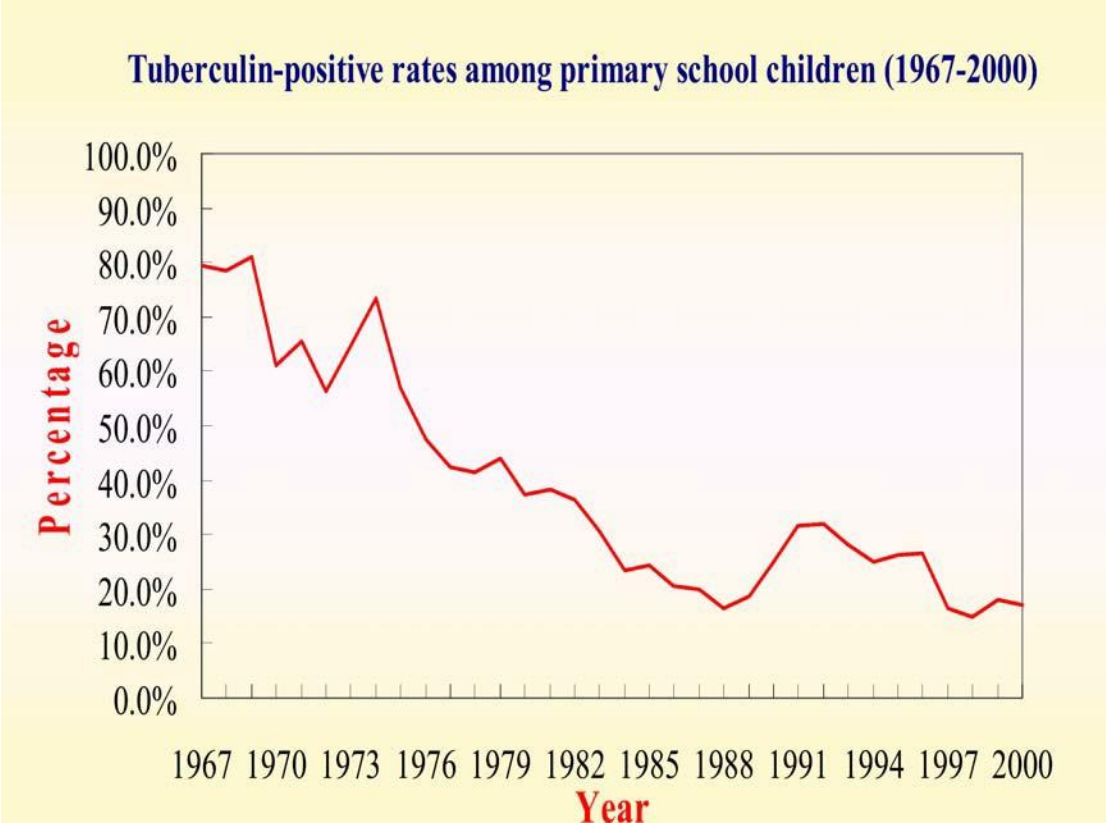

Figure 3. Tuberculin-positive rate among the 6- to 9-year olds from 1967 to 2000

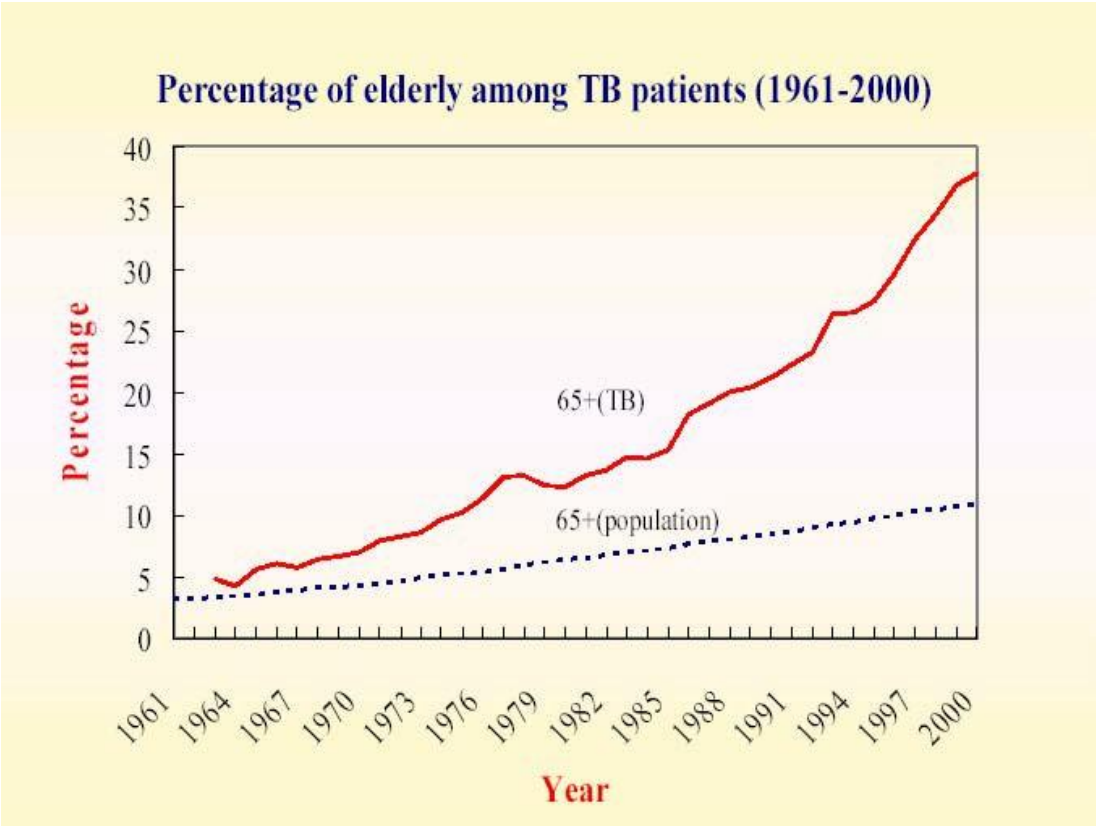

Figure 4. Proportions of elderly among TB patients and among the population

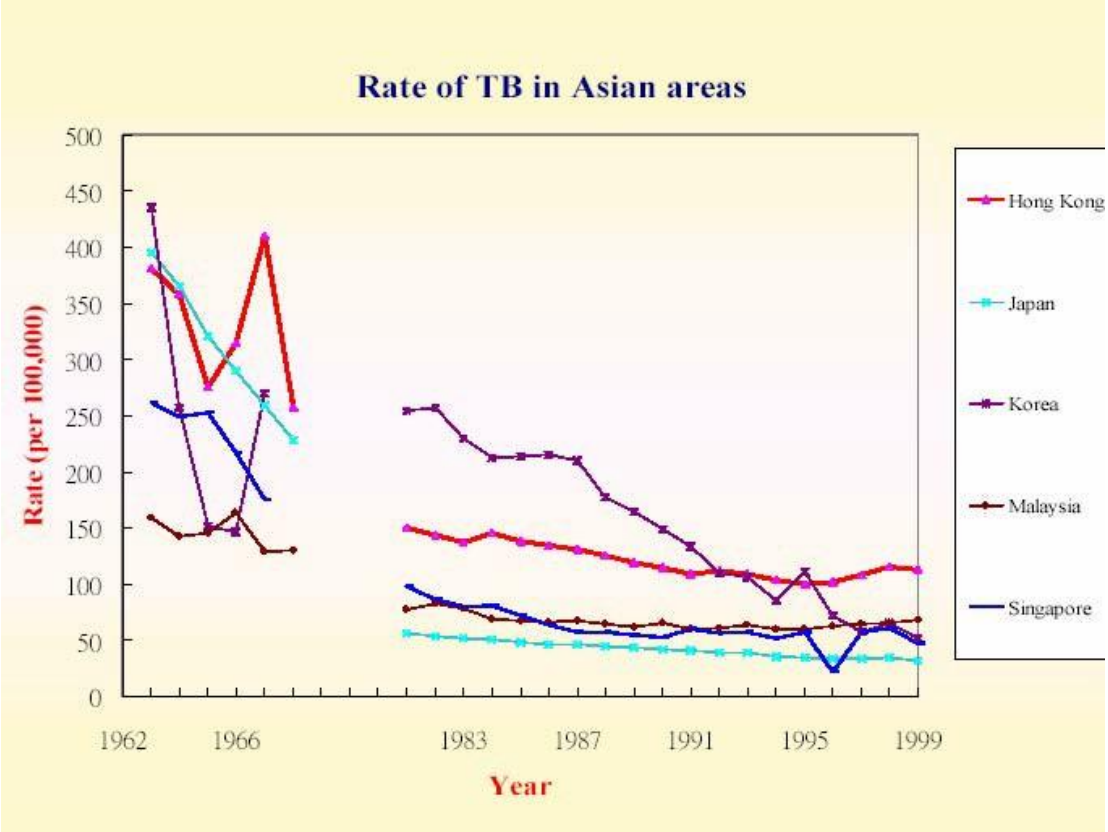

Figure 5. TB rates in developed Asian areas (intermediate burden areas)

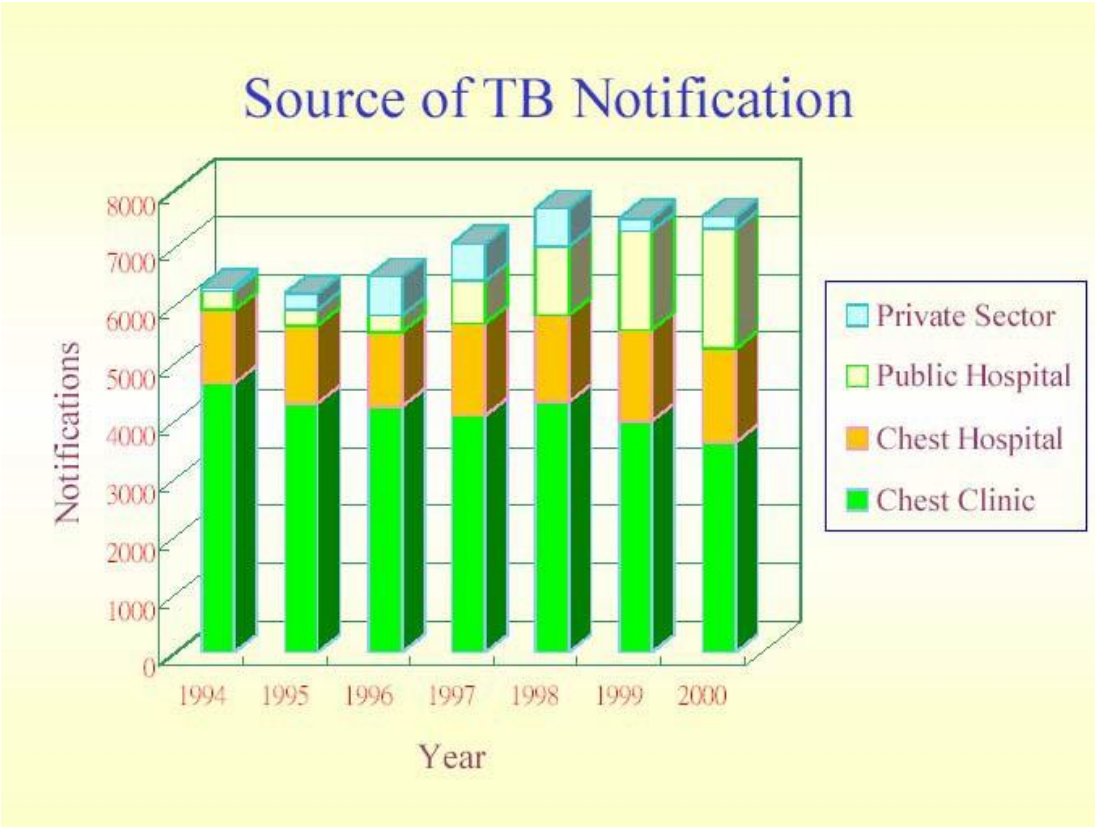

Figure 6. Sources of TB notification

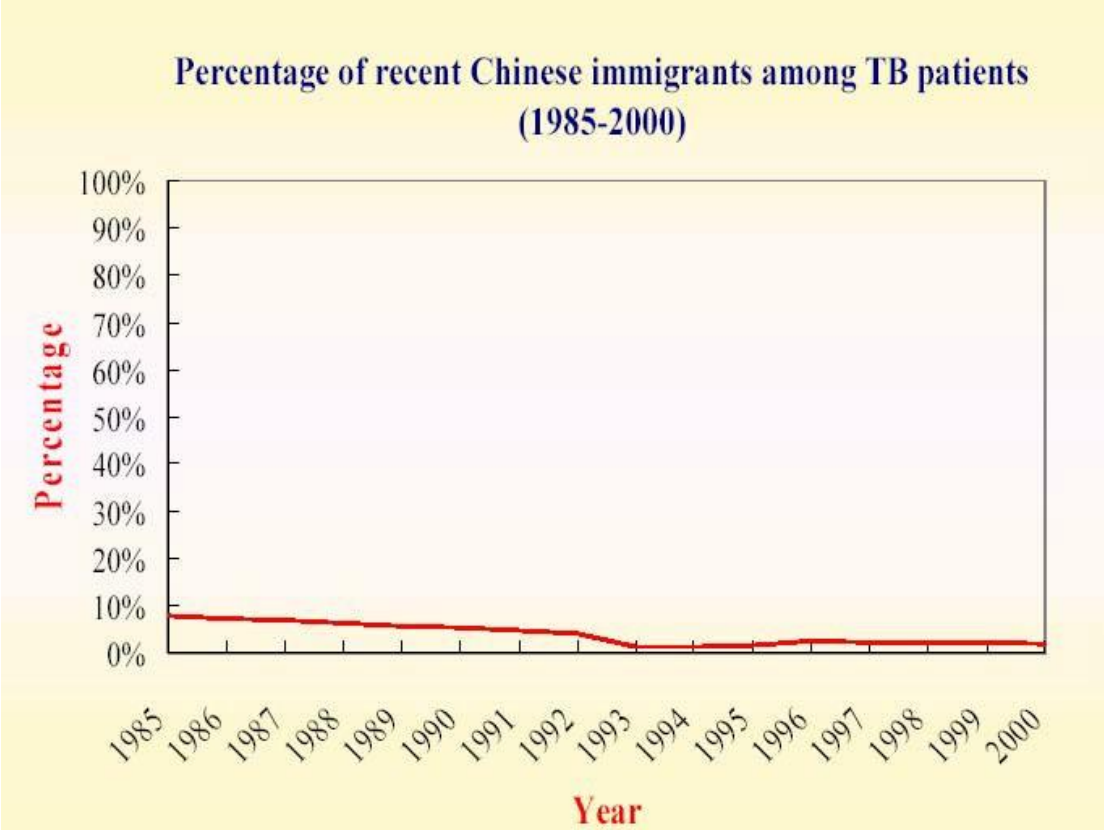

Figure 7. Percentage of recent Chinese immigrants among TB patients (1985-2000)

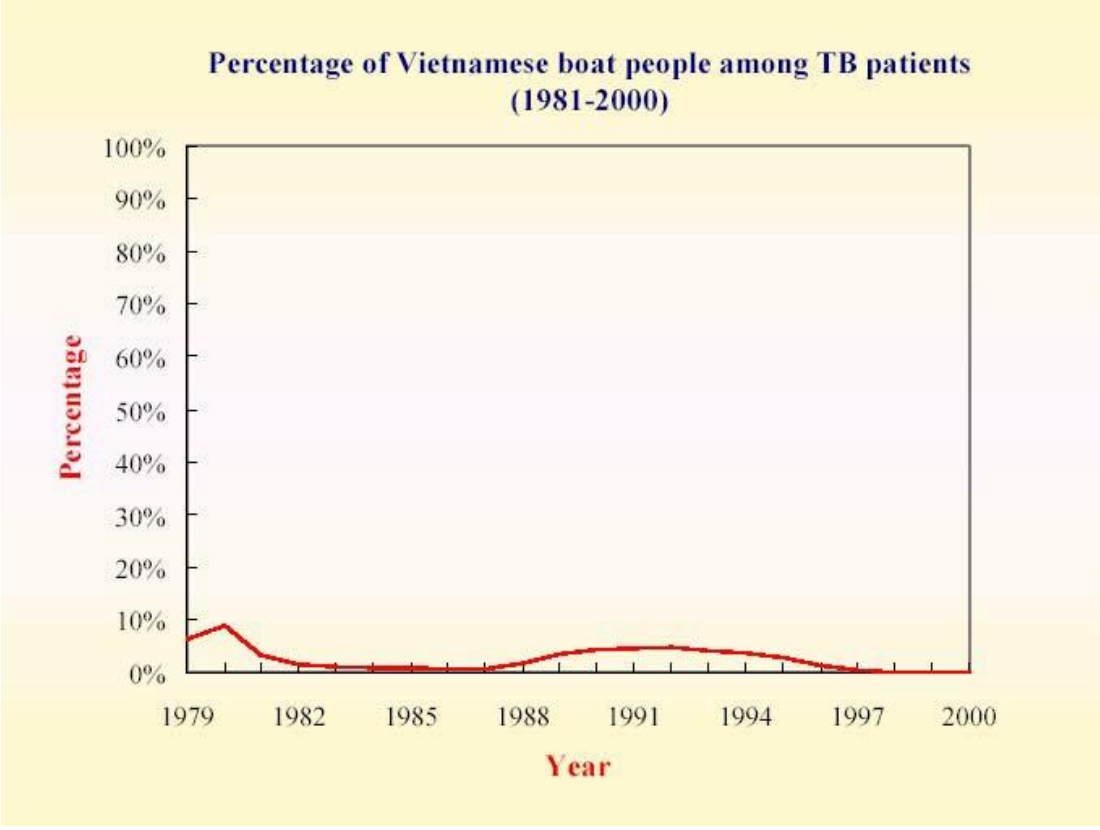

Figure 8. Percentage of Vietnamese boat-people among TB patients (1979-2000)

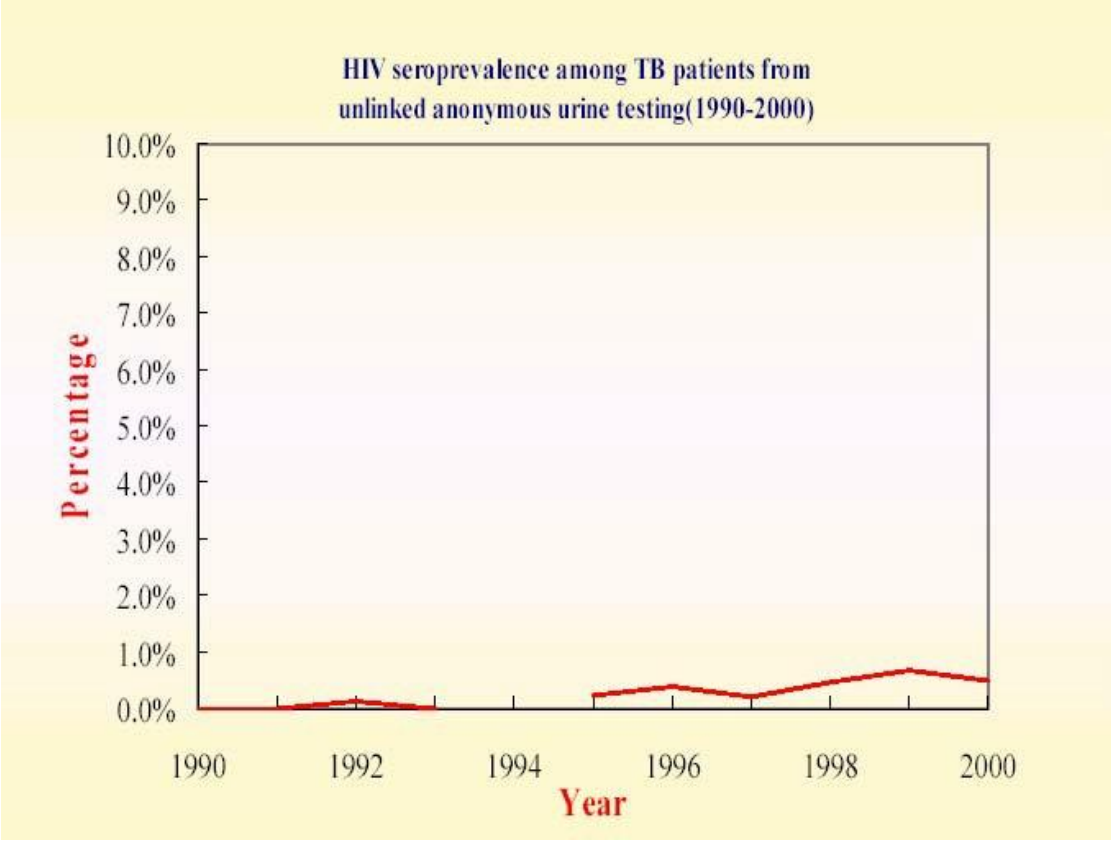

Figure 9. HIV seroprevalence among TB patients from unlinked anonymous urine testing

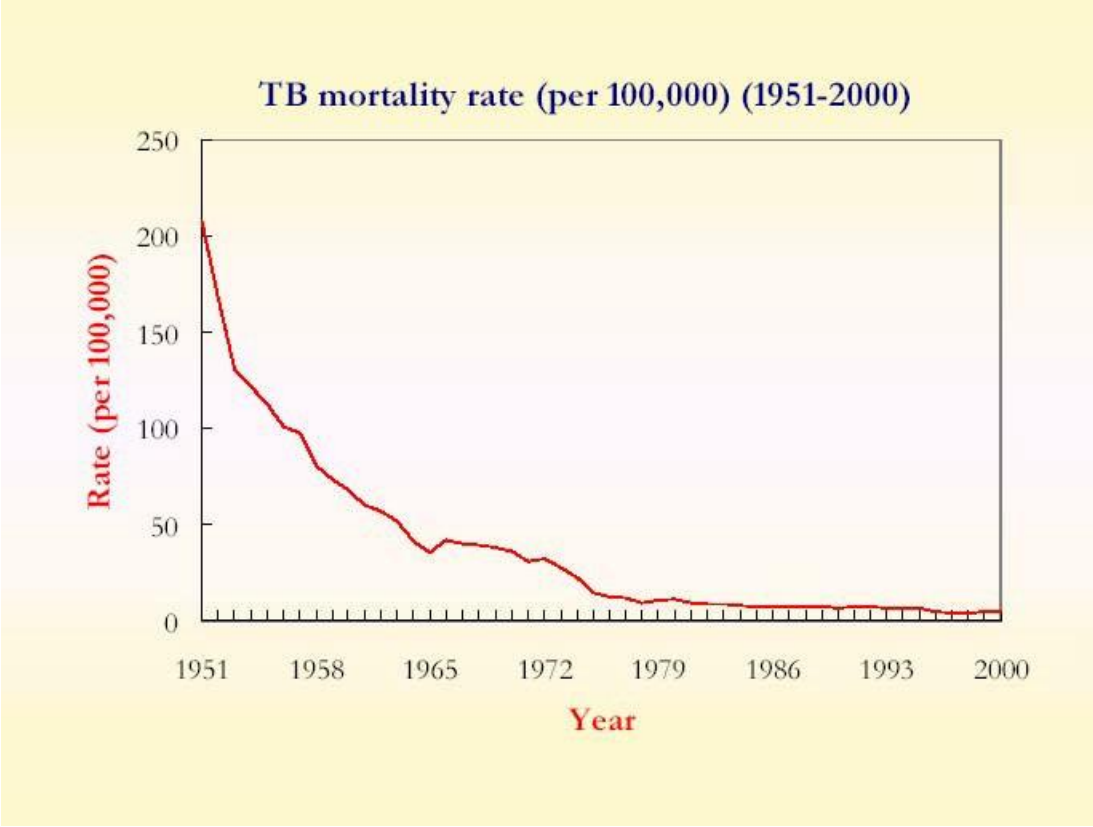

Figure 10. TB mortality rate from 1951 to 2000

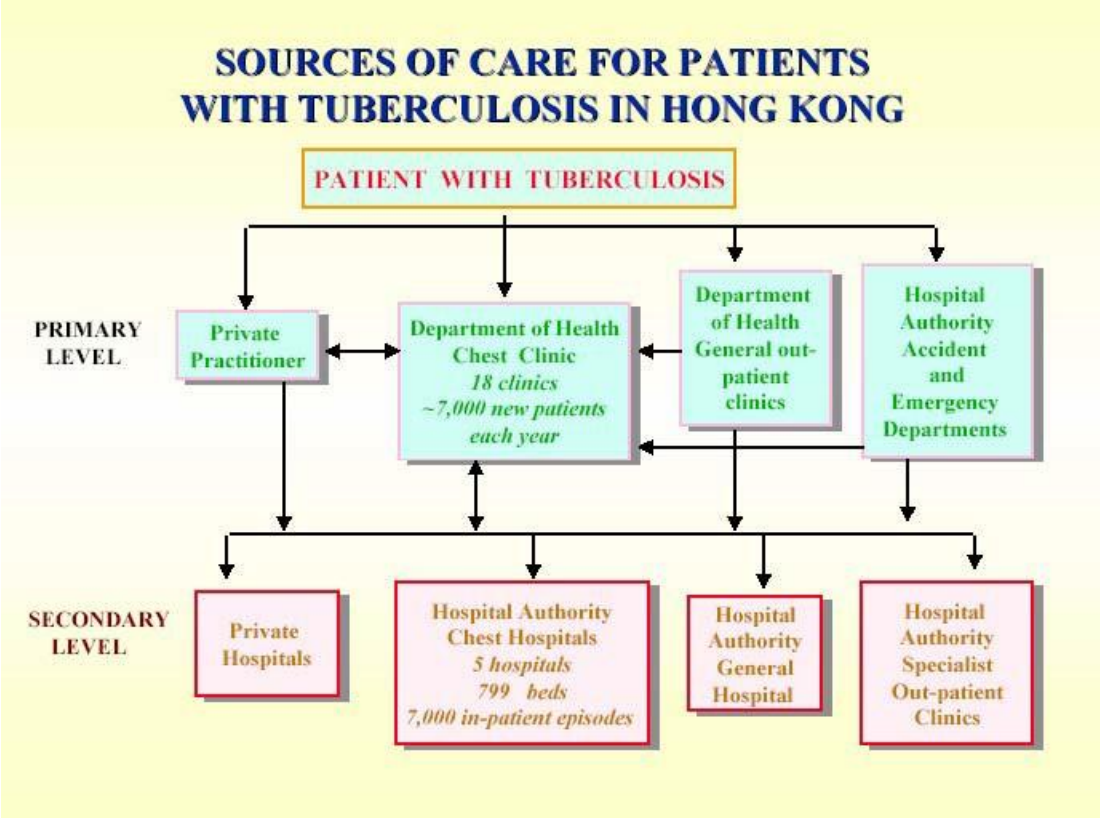

Figure 11. Sources of care for patients with tuberculosis in Hong Kong

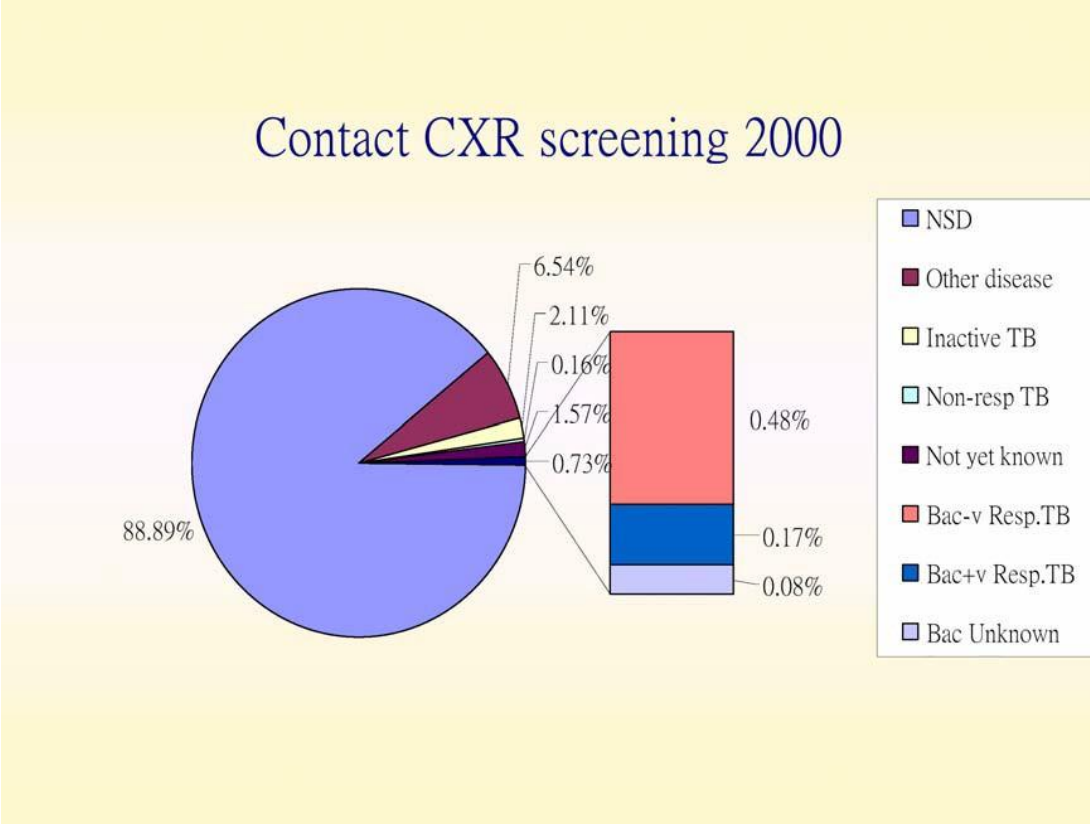

Figure 12. Yield of contact CXR screening in 2000

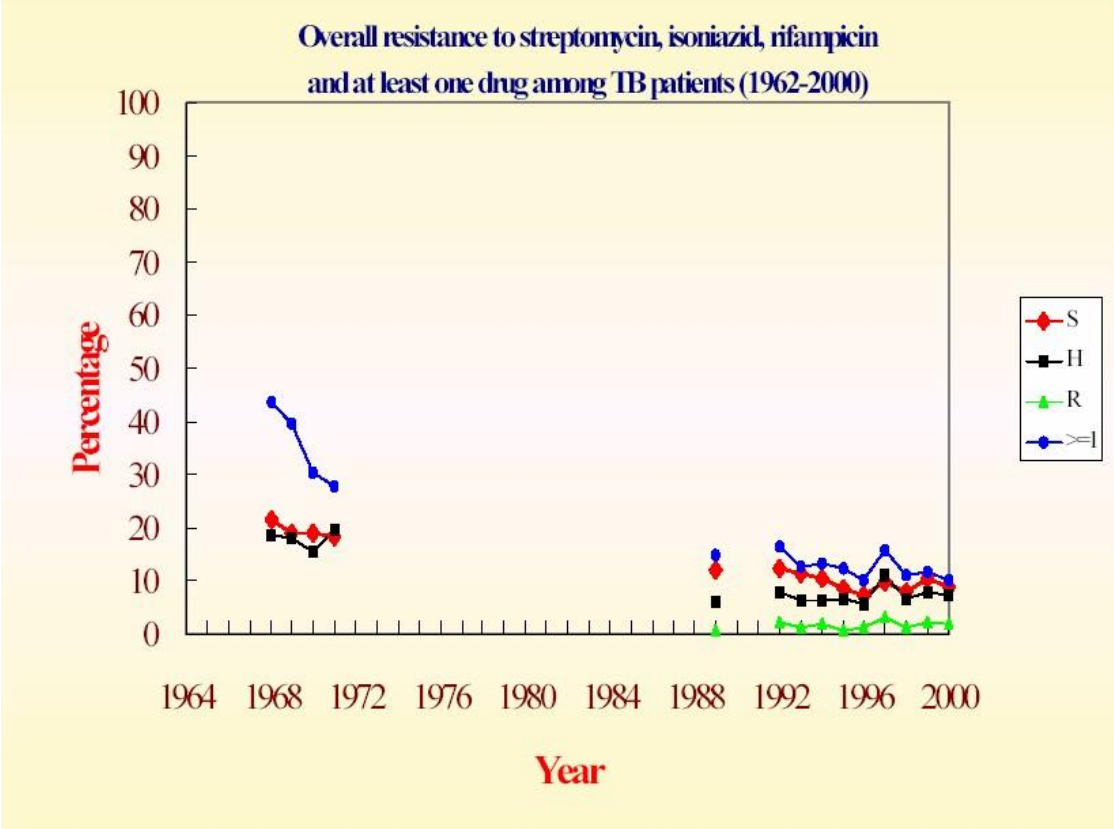

Figure 13. Trend of resistance to anti-TB drugs

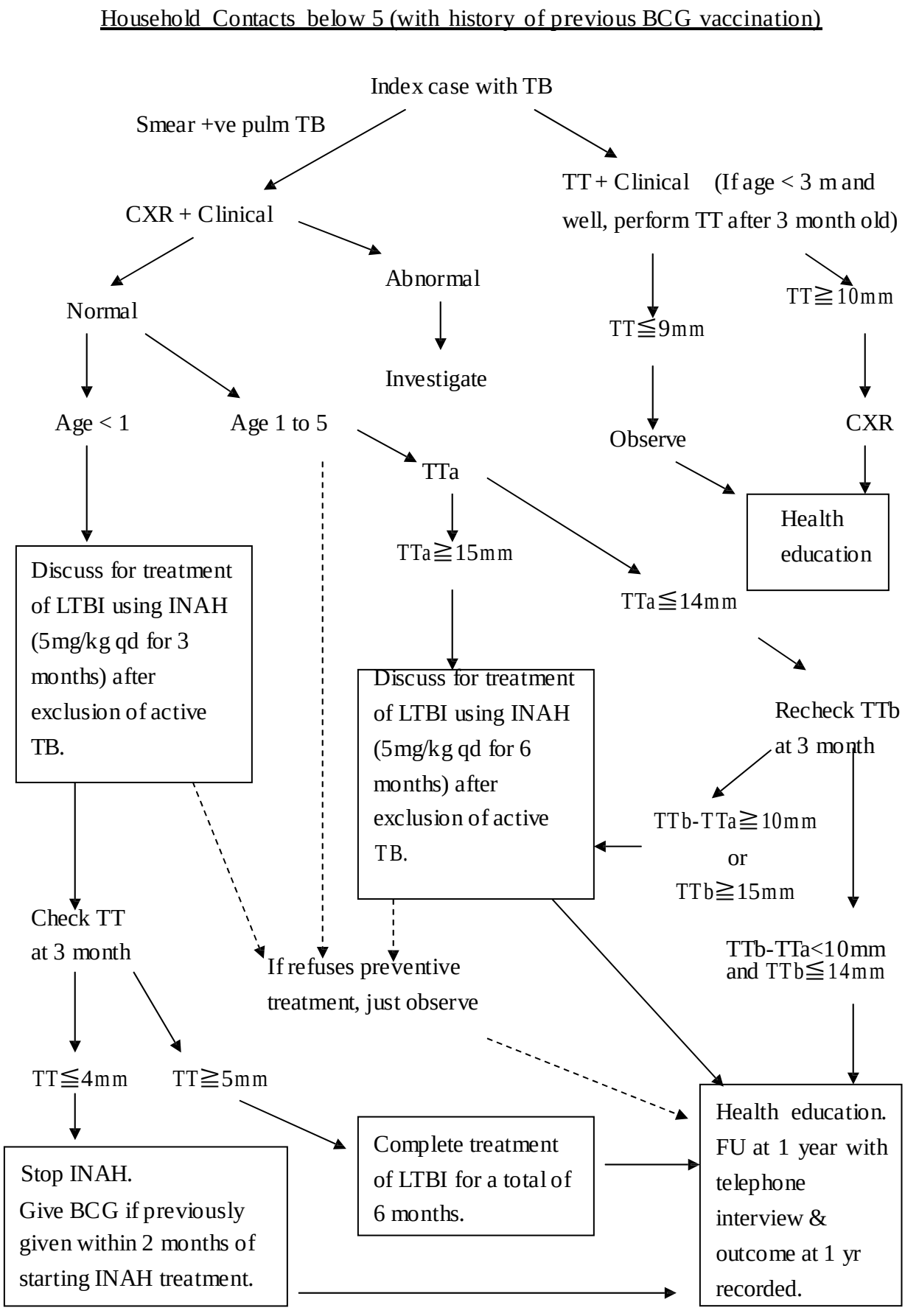

Figure 14. Protocol for treatment of latent TB infection among BCG-vaccinated household contacts

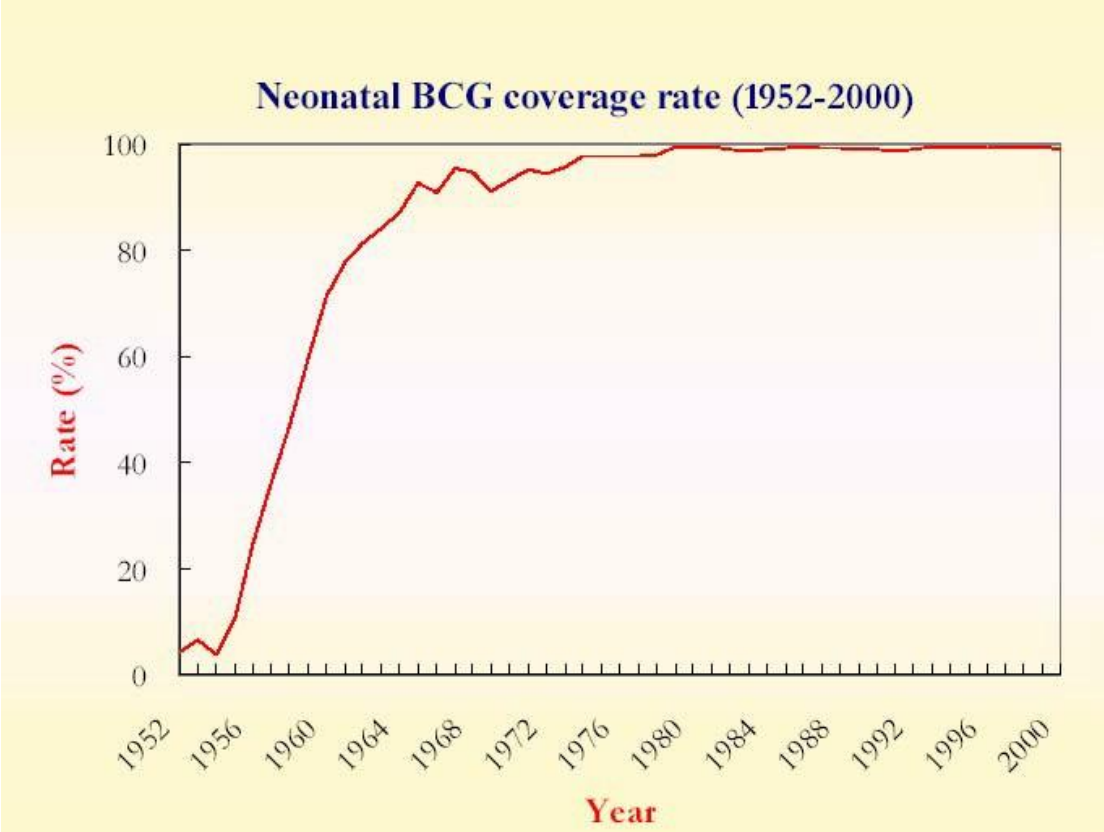

Figure 15. Neonatal BCG coverage rate from 1952 to 2000

(Extracted from Government Chest Service Annual Report 2000)