[Environmental Health and Preventive Medicine 10, 213–218, July 2005]

Commentary

Japan's National Tuberculosis Control Strategies with Economic Considerations

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Abstract

We made a bibliographic search for Japanese and non-Japanese literature on tuberculosis control programs to study the current public health policies for tuberculosis control in Japan especially in regard to cost-effectiveness. Then, we compared the Japanese strategies for tuberculosis control with those in other countries including the United States, and those recommended by World Health Organization (WHO). The current trend of tuberculosis incidence in the Japanese community demonstrates major differences from the situation that had prompted installation of tuberculosis control measures several decades ago. The tuberculosis control measures should be targeted to the elderly people (over 65 years old) because of the following three aspects. (1) A continuing decline of tuberculosis in the young Japanese population, particularly children who might attain benefits from BCG immunization; (2) The enhancement of the prevalence among the elderly people who are not covered by a uniform national surveillance strategy; (3) Cost-ineffectiveness of Mass Miniature Radiography (MMR) being used as a means to screen for tuberculosis. The cost-effectiveness issue must be considered more seriously, and the WHO recommendations especially in regard with the DOTS (directly-observed treatment, short course) strategy need to be incorporated more effectively into the national program since the incidence of drug resistant tuberculosis in Japan has been recently increasing. Finally, we propose to limit BCG immunization further and to discontinue annual MMR in the young population, and instead to develop effective strategies of both active and passive case finding in the elderly through public and community health services.

Key words: active case-finding (AFC), BCG immunization, mass miniature radiography (MMR), sputum smear examination, tuberculosis (TB)

Introduction: overview and objectives

Following the recent resurgence of tuberculosis cases all over the world, new strategies or a revision of previous policies has been considered by different health care systems. Epidemiological factors, especially the spread of HIV infection, and the growth of the elderly population in developed countries like Japan, have a significant role in the need for such revisions (1, 2). Also the ever-increasing awareness of the cost effectiveness and cost opportunity issues requires policy makers to pay more attention to these aspects of public health programs (3). Considering the obviously "changed" epidemiological trend of tuberculosis infection and disease in the Japanese population, changes in the preventive strategies may be needed in the current situation, which is far different from when these strategies were implemented (Figs. 1, 2).

Controversies over the national BCG immunization program in Japan (4) finally lead to a decision to revoke the school age BCG revaccination of Japanese children from April 2003. BCG immunization is still practiced for infants while the annual risk of tuberculosis infection in Japan has been estimated around 0.05% in the 1990's (5), namely much lower than the widely recognized index of 1% to recommend such a preventive measure at the national level. Although there is good evidence that BCG vaccination can prevent severe complications of tuberculosis infection in children (under 15) and especially infants (as of meningitis and miliary TB), considering the scarcity of such extreme cases in recent years in the Japanese population (0.1 or less per 100,000) the cost per death or

Received Dec. 2, 2004/Accepted May 2, 2005
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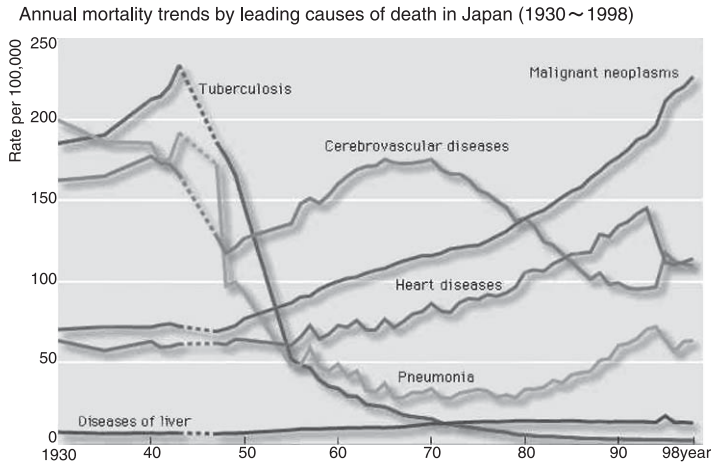

Fig. 1 The significance of TB as a major cause of death through the years, from the 1930–40's to the 1990's, compared with other causes. (Source: The National Cancer Center (NCC), Japan)

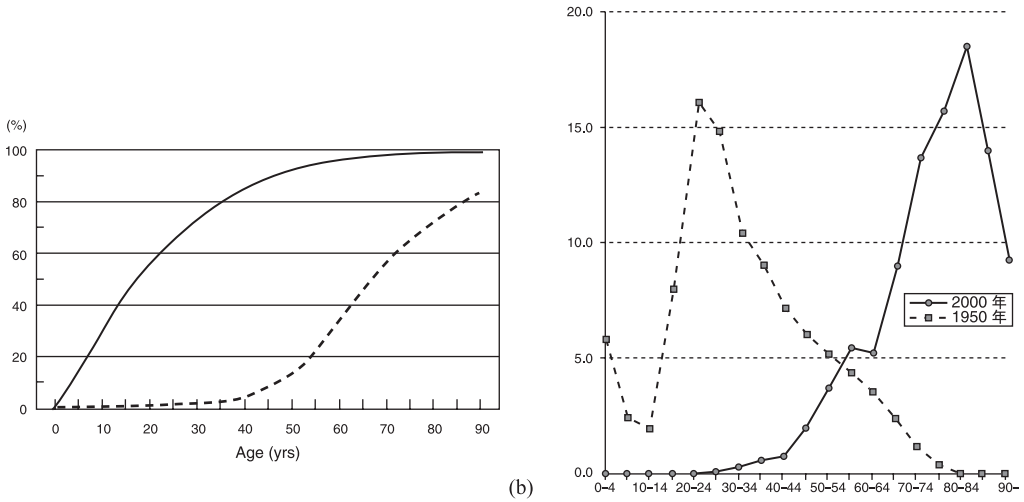

Fig. 2 (a) Cumulative prevalence of TB infection by age in 1950 (solid line) & 1995 (dashed line) and (b) the age distribution of TB mortality in 1950 (dashed line) & 2000 (solid line) show a sharp decrease in Japan for all ages especially children but a recent relative increase in the +65 age group. (Source: Research Institute of Tuberculosis, Japan Anti Tuberculosis Association)

disability averted is relatively high (6). In fact, the worrisome figures relate to a recent increase of tuberculosis cases in the elderly who get no benefits from any BCG immunization (e.g., as of revaccination) program (Fig. 2).

The Role of BCG Vaccination in Tuberculosis Control Programs

Vaccination with BCG does not necessarily prevent tuberculosis but raises a person's resistance to TB. In 1993 and 1994, two meta-analyses on the results of BCG vaccine clinical trials and case control studies confirmed its high (>80%) protective efficacy at preventing serious forms of TB in children especially against meningeal and miliary tuberculosis (7–9). Basically, BCG vaccination can help protect infants in communities with a reasonably high risk of infection.

In August 1995, the WHO issued a statement on BCG vaccination with the following recommendations (10): First, in countries with a high prevalence and incidence of tuberculosis, BCG vaccination should be given to infants as soon after birth as possible. Second, if tuberculin testing is used to make decisions on BCG revaccination, the practice should be discontinued. Third, repeat vaccination is not recommended and multiple revaccinations are not indicated at all. As for the "high" limit referred to in WHO's recommendation, the risk of infection is the most informative indicator of the epidemiological situation of tuberculosis and its trend and related to the number of infectious sources in the community. Assuming that each active case of tuberculosis infects on average 10 persons a year, a 1% annual risk of infection[1] corresponds to an incidence of 100 sputum smear-positive cases per 100,000 people. Considering that each active case is on average infectious for two years, 2,000 transmissions of infection may occur in such a population to infect 2% of the population. So BCG immunization is gener-

[1] The average annual risk of infection with tuberculosis may be calculated from a tuberculin skin test prevalence survey, as the true incidence is difficult to measure. The risk of infection that is calculable from the prevalence of infection is thus an average annual risk, and is a proxy for the incidence of tuberculosis infection.

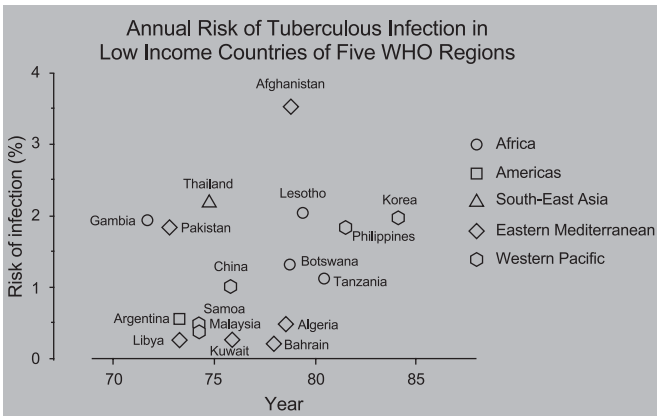

Fig. 3 The estimated annual risk of infection in a group of low- and middle-income countries varies from less than 0.5% to about 4%. (Cauthen GM, et al. WHO document 1988; WHO/TB/88.154: 1–34)

ally considered for the communities where the annual infection rate is above 1% and other control measures have proved ineffective (Fig. 3).

On the other hand, the difficulties in interpretation of a positive tuberculin reaction in the BCG immunized can lead to high costs of using alternative diagnostic methods. The costs of BCG vaccines and their injection, resorting to costly tests to exclude a TB diagnosis in suspected cases, and the costs of any side effects of the vaccines (about 2%) should all be counted. There is also the potential of neglect in detection due to the common misperception of laypersons that their BCG vaccinated children are immune to tuberculosis; an inquiry into the significance of such a hazard merits a social study on the knowledge of a random group of parents.

In USA where the prevalence of tuberculosis infection in infants is higher than in Japan, CDC guidelines do not recommend BCG vaccination for immunization programs or TB control programs. BCG revaccination was discontinued in Hong Kong (11, 12), from the school year 2000/01, following discussions with the Advisory Committee on Immunization (ACI); it was decided to continue BCG vaccination for newborns but to stop BCG revaccination as there was no evidence for its efficacy (Table 1).

The "opportunity cost" of BCG immunization on TB screening in Japan is the loss of the tuberculin test as a very inexpensive but highly accurate means of case detection. This test is widely used for this purpose in other developed countries (13, 14). BCG vaccination decreases both the sensitivity and specificity of tuberculin test and functions as a compounding factor in tuberculosis screening activities.

Table 1 A comparison of BCG revaccination policies in Japan with some of its neighbors & other countries

BCG Revaccination Program	Countries/Areas
Not practiced even before WHO's statement in 1995	Thailand, Sri Lanka
Stopped after WHO's statement in 1995	Taiwan, The Philippines, Republic of Korea, Beijing, Shanghai, Guangdong
Under review/change	Singapore, Japan
Program being continued	Malaysia
Primary vaccination limited, no revaccination	Australia, United Kingdom, USA

Adverse reactions to the vaccine are more common in young infants than older children (15). Moderately severe reactions, such as marked lymphadenitis or suppurative adenitis, occur in 0.2 to 4.0 per 1,000 vaccinations but fatal reactions are very rare (#1 in 1 million vaccinations).

Mass Miniature Radiography (MMR)

The method of case finding practiced in Japan according to the TB prevention law since 1950's is based on periodic Mass Miniature Radiography (MMR) in schools and institutions and communities. MMR is similar to general radiography except for the dedicated X-ray equipment, and the smaller x-ray film (10×10 cm). In 1951, when the TB prevention law was implemented, the number of TB patients was 590,662 across the nation (16). This number drastically dropped over the years. In 1960, from approximately 38,838,000 people taking the annual X-ray, 0.4% were found to be TB patients (17). But in recent years, the number of those receiving the annual test is about 25 million with only about 2745 (±216) positive for TB (17). In 1998, the percentage of cases detected by MMR among newly notified cases of TB was 12.8%, almost constant for the last 10 years (18). Though the idea is to find patients who discharge TB bacilli and infect others, only 35.1% of the cases found by MMR in Japan were confirmed by bacteriology (18). The detection rate of MMR as of 1998 was 0.03 per 1000 school children, 0.06 per 1000 employees, and 0.016 per 1000 community citizens, with a cost per TB case detected of 4.4 million yen for all cases, 2.3 million yen for males, 8.4 million yen for females, 7.3 million yen for 40–49 year old people, and 1.8 million yen for those over 80 (18). After correlation with the TB incidence rate in different areas of Japan, the cost of MMR was 4.0 million yen per case in areas with an incidence rate of 30 per 100,000, and 6.7 million yen in areas with an incidence rate of 20 per 100,000. Ohmori et al. concluded that MMR was not economically cost-effective even among the elderly as the medical expense of treating a TB patient with 2 months of inpatient care and 4 months of outpatient care was about 0.9 million yen (1996 data).

Moreover, only about 5 to 10% of those infected with TB develop tuberculosis in their lifetime and the other 90% will never become sick or infectious to spread the infection to other people. In Japan, there are plans to reduce the use of MMR by only requiring those up to the age of 40 to have it when they start a new job or are transferred. Currently people over 16 are obliged to receive X-ray tests annually.

Norway has had an interesting experience in their tuberculosis surveillance system having used mass miniature radiography (MMR) to detect active pulmonary tuberculosis as early as of 1943, with coverage of the whole population by 1952 (19). But in 1975, they implemented a countrywide *selective* case finding program using a mathematical model for assigning a tuberculosis risk score to each individual to determine the selection. This way, the screening initially covered 30% of the population screened and by 1996 was further reduced to only 3.5%. Even so, the percentage of cases identified by chest X-ray

screening was 12.2% in 1975 and 6.2% in 1995 (19). It is worth noting that Norway has one of the lowest TB incidence rates among developed countries. A study in Australia (20) concludes if the goal is the *elimination* of the disease, then judicious use of MMR can contribute to TB case finding even in low prevalence countries.

An Alternative Case-Finding Program at Community Sources of Infection

The basis of alternative screening tools in TB control programs is the fact that the best way to prevent TB is to find and cure TB infectious cases, as each such person infects several persons in each year. Sputum smear positive patients are the major sources of transmission of tubercle bacilli in the community. In a study of the proportion of transmissions attributable to smear positive and smear negative cases (Fig. 4), sputum smear examination proved to be a very sensitive tool to identify *sources of infection*. The sputum smear examination is done after an inquiry into a set of symptoms the most important of which is a cough persisting for 3 weeks or more. In some studies, active case finding on a single chronic cough question has been suggested as the most successful for identifying active cases in the community (21). In other studies, the presence of weight loss and/or chronic cough was found to be particularly sensitive (22). In still others, they look for cough (between two and four weeks), hemoptysis, weight loss, fever, night sweats, and/or generalized weakness (23). Strategies to identify TB suspects differ widely among various countries and have included interviewing of the elderly, surveys of households, contact tracing among registered patients and TB suspects, and public broadcast messages; but the primary method of screening in most studies has been smear microscopy. Some have recommended multiple smears but it becomes less cost effective and may be unnecessary (24). Sputum culture is very specific and more sensitive than microscopy but takes time and is relatively expensive. High-risk groups in a community can be the targets of such an active case finding program. In Africa for example, HIV positive people are the major target. As for Japan, information from tuberculosis surveillance systems could identify high-risk groups for targeted interventions: the elderly (the exact limit, different for urban versus rural areas can be determined through statistical data), the homeless, recent immigrant workers from high risk countries of the South-East Asian region (25), factory workers exposed to silicosis, the HIV infected, workers and residents of long-term care facilities (nursing homes, prisons, etc), health care workers, the malnourished, alcoholics, and also those in close contact with individuals known to be TB infectious (26–28). Improving the passive case finding and better access to treatment has also been recommended.

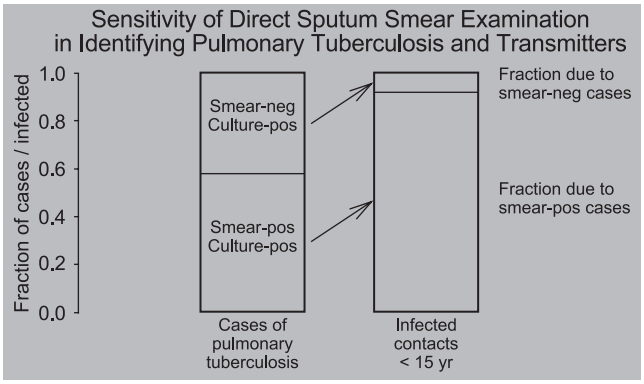

Fig. 4 Smear examination is a very sensitive tool to identify sources of Tuberculosis infection. (From data gathered by Grzybowski S, et al. Bull Int Tuberc Lung Dis. 1975; 50: 90–106)

Further Discussion and Conclusions

A cost-effectiveness analysis of TB control programs requires consideration of the total costs of TB control (for a given population over a given time period), the number of deaths and the morbidity that would occur due to tuberculosis in the absence of control and with the control program. The benefits of the control program depend on a variety of factors, including the average age at which individuals develop TB, the average life expectancy of a TB patient if cured, and the TB incidence and prevalence rates. Arguments have been made against active case finding based on studies done in the 1970's in Europe and Japan where only 15 to 25% of new smear-positives were detected by active case-finding programs. The measures of effectiveness of tuberculosis control programs based on the system's reliance on BCG immunization or active case finding can be compared as in Table 2.

In Japan, the era when tuberculosis was referred to as the "national disease" is over, thanks to higher standards of living, and medical and pharmaceutical advances. But in recent years, Japan has come to face serious TB problems of a different nature, including the growing incidence of tuberculosis among the elderly and foreign residents in Japan (29), and the emergence of strains resistant to multiple drugs. It might be expected that the growth of Japan's elderly population will increase the incidence rate of tuberculosis further, unless some new strategies are set into action.

The discontinuation of BCG revaccination of Japanese school age children implemented from April 2003 appears to be a right step both on the grounds of cost minimization and the scarcity of any clinical benefits for such a policy. The cost effectiveness studies by Japanese researchers as an economic evaluation of universal BCG vaccination of Japanese infants

Table 2 A comparison of the two TB control programs based on BCG and an alternative active case finding (ACF) by some measures of effectiveness

	BCG	ACF
Prevention of TB	+	+++
Prevention of death	+	++
Helping with diagnosis	–––	+++
Prevention of multi-resistance	–	+
Complications & their costs	+	–
Creating social awareness	–	+
Total costs to the system	++	?

–, +, ++, and +++ help to define effectiveness as lacking, slight, intermediate and considerable, in that order.

found it more costly than treatment, as in the case of MMR for case finding. But further moves should be brought into discussion. A general discontinuation of BCG immunization can be considered and thereafter the use of the tuberculin test reserved as a screening tool for tuberculosis infection, and no longer as a criterion of the need for revaccination. Trials of active tuberculosis case finding programs in high-risk groups of the community, especially the elderly (above 65), homeless & immigrant workers from epidemic areas may provide better guidelines; with sputum smear microscopy in those physically capable of producing sputum being a more effective and less costly tool than MMR. A cost evaluation study to search for an optimum TB control program in Japan can be recommended to help define more exact criteria for screening, as for definition of high-risk groups and residential areas in different prefectures. More emphasis should be laid on directly observed therapy in short courses (DOTS) by health-care providers. Analyses of national programs in ten provinces of China showed that this strategy is both effective and cost-effective and based on the success of these programs, the World Health Organization (WHO) adopted DOTS as its strategy for global tuberculosis control. But since WHO's recommendation of the DOTS strategy, uptake by national programs has been slow, so that only 11% of new smear-positive pulmonary tuberculosis cases were enrolled in DOTS programs worldwide in 1997 (Kochi et al. 1997). Still it is unlikely that considerable gains against tuberculosis can be achieved through promotion of the DOTS strategy alone.

In short, we believe it may be more clinically relevant and also cost effective to exclude BCG immunization from the Japanese TB control program (and gradually advocate the tuberculin test as a screening tool), stop the practice of Mass Miniature Radiography (MMR) for case finding in young Japanese, and instead enhance public health programs for passive case finding and the management of their treatment through the DOTS strategy, and plan pilot studies on active community case-finding programs directed at specific high-risk target groups among the elderly.

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